GLOBAL MEDICAL & HEALTH COMMUNICATION

Global Medical and Health Communication

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Global Medical and Health Communication

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The submitted manuscript must be the article that has never been published, and the author must ensure that all co-authors have agreed by signing a statement on the seal. For original research, we accept the study which is last then 7 (seven) years when the manuscript is submitted. The manuscript is an original article free from plagiarism. When the article published in another journal then in the next journal, the article will be disallowed.

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Table title is the typed center, font size 10 pt, bold, initial letter of each word written with capital letter, except conjunctions. The titles are numbered and written on top of the table. Example: Table 3 *Neisseria gonorrhoeae* Resistance to 8 Types of Antimicrobials in 20 Specimens. Table, no vertical dividing line, and there are only three horizontal borderlines. Created tables in sequence two spaces from the text. Table descriptions and abbreviations are placed in the table description, not on the table title.

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The article contains results of original research in the field of basic medical or applied, and health. The article format consists of Title & Abstract (English) and *Judul & Abstrak* (Indonesian), Introduction, Methods, Results, Discussion, Conclusion(s), Conflict of Interest, Acknowledgments, and References.

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Maximum article title consists of 12 words (choose words and terms that are dense meaning and able to characterize the entire contents of the script). Typed with bold fonts, size 12 pt, one space, the initial letter of each word is written in capital letters (except the conjunctive), and center. The ownership row consists of 2 elements, the author name and origin institution. Author's name written with the initial fonts are capital and bold, size 11 pt, one space, and center. Institution name written with the initial fonts are capital, size 10 pt, one space, and center.

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The introduction is written succinctly to stimulate the reader's interest include all the necessary information. At the end of the introduction was written the purpose of the study.

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The result is the core of scientific writing. This section presents data and information that will be used as

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Discussion of the article reveals, explains, and discusses the results of the study with an analysis by the research design, interpretation, and explanation of its synthesis. Also, the results obtained are compared with the results of previous research of others.

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The conclusion is submitted by the results obtained by the researcher and written briefly and clearly in two or three sentences.

Conflict of Interest
All authors must make a formal statement at the time of submission indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include, but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product.

Acknowledgment
Acknowledgments should be provided to research contributors without writing a degree.

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Zhang B, Kunde D, Tristram S. *Haemophilus haemolyticus* is infrequently misidentified as *Haemophilus influenzae* in diagnostic specimens in Australia. Diagn Microbiol Infect Dis. 2014;80(4): 272–3.

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Editor as Author
Nriagu J, editor. Encyclopedia of enviromental health. Michigan: Elsevier BV; 2011.

Organization as Author
World Health Organization. Guideline: neonatal vitamin A supplementation. Geneva: WHO Press; 2011.

Chapter in Book
Miller LG. Community-associated methicillin resistant *Staphylococcus aureus*. In: Weber JT, editor. Antimicrobial resistance. Beyond the breakpoint. Basel: Karger; 2010. p. 1–20.

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Nicholai T. Homeopathy. Proceedings of the Workshop Alternative Medicines; 2011 November 30; Brussels Belgium. Brussels: ENVI; 2011.

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King P. *Haemophilus influenzae* and the lung (*Haemophilus* and the lung). Clin Transl Med. 2012;1:10 [cited 2015 August 15]. Available from: https://clintransmed.springeropen.com/articles/10.1186/2001-1326-1-10.

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RESEARCH ARTICLE

Halal Critical Point Analysis of *Bajakah* Wood (*Spatholobus littoralis* Hassk.) Nano Particle as Anticancer Agent

Lelly Yuniarti,[1] Yuktiana Kharisma,[2] Titik Respati,[3] Maya Tejasari[4]
[1]Department of Biochemistry, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[2]Department of Pharmacology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[3]Department of Public Health, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[4]Department of Histology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

Bajakah wood contains phenolic compounds, flavonoids, tannins, and saponins with anticancer activity. The discovery and development of new drugs require several stages. In the process, there are many possibilities of adding other substances to form new active substances or as solvents that allow drug preparations to be doubtful of halalness. Hence, it is necessary to analyze the critical point of halal ingredients. The purpose of this study was to determine the characteristics of the nanoparticles of *bajakah* wood (*Spatholobus littoralis* Hassk.) and to test the anticancer activity in several cancer cell cultures, as well as to analyze the critical point of halalness of the material. This research method is a composition test using chromatography and anticancer activity test using MTT. Analysis of the critical point of halal materials using hazard analysis critical control point (HACCP). The research was carried out at the Indonesian Engineering Nanotechnology Laboratory South Tangerang and the UGM Integrated Laboratory Sleman in July–December 2020. The results showed that bajakah wood nanoparticles contained pure water as a solvent, viscosity 0.08878 cP, scattering intensity 1.1059 cps, diameter 176.1+/−43.7 (nm). Cytotoxic test results showed IC50 against cell culture MCF7 1,063.28 (±114.98) g/mL, HepG2 53.34 (±0.35) g/mL, T47D 150.63 (±8.44) g/mL, WiDR 114.38 (±7.82) μg/mL, HTB 97.50 (±3.49) μg/mL, HeLa 182.95 (±36.22) μg/mL, and Vero 710.10 (±106.46) μg/mL. This study concludes that *bajakah* wood nanoparticles are not critical in terms of halal ingredients. At the same time, their anticancer activity is weak against breast cancer and uterine cervical cancer, medium categories against liver cancer and lung cancer, and is not toxic to normal cells.

Keywords: Anticancer, *bajakah* wood, critical halal point, nanoparticle

Analisis Titik Kritis Kehalalan Nanopartikel Kayu Bajakah (*Spatholobus littoralis* Hassk.) sebagai Agen Antikanker

Abstrak

Kayu bajakah mengandung senyawa fenolik, flavonoid, tanin, dan saponin yang memiliki aktivitas antikanker. Penemuan dan pengembangan obat baru memerlukan beberapa tahapan. Dalam prosesnya terdapat banyak kemungkinan penambahan zat lain untuk membentuk zat aktif baru atau sebagai pelarut yang memungkinkan sediaan obat diragukan kehalalannya. Oleh sebab itu, perlu dilakukan analisis titik kritis kehalalan bahan. Tujuan penelitian ini mengetahui karakteristik sediaan nanopartikel kayu bajakah (*Spatholobus littoralis* Hassk.) dan menguji aktivitas antikanker pada beberapa kultur sel kanker, serta menganalisis titik kritis kehalalan bahan. Metode penelitian ini adalah uji komposisi menggunakan kromatografi dan uji aktivitas antikanker menggunakan MTT. Analisis titik kritis kehalalan bahan menggunakan *hazard analysis critical control point* (HACCP). Penelitian dilakukan di Laboratorium Nanovasi Rekayasa Indonesia Tangerang Selatan dan Laboratorium Terpadu UGM Sleman pada Juli–Desember 2020. Hasil penelitian menunjukkan sediaan nanopartikel kayu bajakah mengandung pelarut air murni, viskositas 0,08878 cP, *scattering intensity* 1,1059 cps, berdiameter 176,1+/−43,7 (nm). Hasil uji sitotoksik menunjukkan IC50 terhadap kultur sel MCF7 1.063,28 (±114,98) μg/mL, HepG2 53,34 (±0,35) μg/mL, T47D 150,63 (±8,44) μg/mL, WiDR 114,38 (±7,82) μg/mL, HTB 97,50 (±3,49) μg/mL, HeLa 182,95 (±36,22) μg/mL, dan Vero 710,10 (±106,46) μg/mL. Kesimpulan penelitian ini bahwa nanopartikel kayu bajakah bersifat tidak kritis dalam kehalalan bahan. Selain itu, aktivitas antikankernya lemah terhadap kanker payudara dan kanker serviks uteri, sedang terhadap kanker hati dan kanker paru, serta tidak toksik pada sel normal.

Kata kunci: Antikanker, kayu bajakah, nanopartikel, titik kritis kehalalan

Correspondence: Dr. Maya Tejasari, dr., M.Kes. Department of Histology, Faculty of Medicine, Universitas Islam Bandung. Jln. Tamansari No. 22, Bandung 40116, West Java, Indonesia. E-mail: mayatejasari4981@gmail.com

Introduction

Cancer is the leading cause of death globally today. In the 21st-century, cancer is considered the most critical barrier to increasing life expectancy in every country globally.[1] Cancer is a progressive degenerative disease characterized by sequential changes in gene expression mediated by genetic and epigenetic changes in the developing tumor cells. The intrinsic complexity and heterogeneous nature of cancer are often exacerbated by an invasive and metastatic progression which is an obstacle to developing effective cancer therapy.[2,3]

To date, the efficacy of chemotherapy, which is an important therapeutic modality for cancer, has not increased because it has side effects and high toxicity, and there is treatment resistance. Therefore, anticancer drugs continue to be developed to obtain a more sensitive and specific treatment to use targeted therapy.[4] The need for new effective drugs for cancer is a commercial opportunity.[3] Efforts to find new anticancer agents are to explore natural ingredients, especially medicinal plants. Indonesia's biodiversity that has the potential as traditional medicine is *bajakah* wood or *bajakah tampala* (*Spatholobus littoralis* Hassk.). Based on the preliminary tests carried out, there were positive signs in the phenolic, flavonoid, tannin, and saponin tests.[5]

The process of drug discovery and development requires several stages, starting from the research process at the preclinical and clinical stages and forming drug preparations. This process involves many stages that allow the process of adding other substances to form new active substances or as a solvent available, allowing the drug preparation to become illegitimate. The reference for Muslims to consume halal products is written in the Quran. There are verses in the Quran that call on Muslims to seek *halal* and *toyibban* in their life. Halal means permissible based on the Quran. *Toyibban* means good, clean, hygienic, and healthy.[6]

Halal food is clean and safe without a trace of impurities and is free from prohibited substances (haram), legally enforced by Islamic law. Muslims must have halal food according to Islamic law with healthy ingredients. The phrase "halal food according to Islamic law or halal food" has a broad meaning. First, the food source is obtained legally and free from theft or corruption—that is ethically halal. Secondly, it must be halal in terms of the type or category of things to

be consumed, such as animals or ingredients contained in any food that Islam approves. That is the physical consideration they allow. Apart from the two conditions above, it also focuses on "processing" or the manufacturing stages starting from slaughtering, washing and cleaning, packaging, storage, transportation, selling, and others. Any practices relating to personnel and premises ensure safety, good manufacturing practices, storage, and distribution. Measures are implemented in the food production chain to ensure that food preparation steps are safe for consumption.[7,8]

Even though the halal industry is receiving much attention nowadays, it still requires many thorough studies. Until now, halal is still often seen as a problem that only involves fiqh scholars. Indeed, the problem of halal and haram is one of the fundamental laws/concepts in Islam. For some people who do not speak Arabic, halal is usually associated with various foods permitted to be taken under Islamic law. Apart from food and beverages, the concept of halal covers a much more comprehensive range of meanings, including behavior, actions, speech, attitudes, clothes, cosmetics, and medicines.[9] The growing religious awareness of consumers has certainly encouraged producers or the industry to convince consumers by providing products. The halal is labeled as a point of sale or branding.[10] Thus, the halal label stamped on the product is one factor that attracts Muslim consumers in making purchase decisions.

One of the product control methods is the hazard analysis critical control point (HACCP). The HACCP is a scientific, rational, and systematic preventive food safety control and supervision management system to identifying, monitoring, and controlling hazards starting from raw materials. It is conducted during the production/processing, manufacturing, handling, and use of foodstuffs to guarantee that the food material is safe when consumed. The HACCP system is defined as a management to ensure the safety of food products in the food processing industry using the concept of a logical (rational), systematic, continuous, and comprehensive (comprehensive) approach. It aims to identify, monitor, and control hazards with high risk to the quality and safe food products.[11] The HACCP concept is rational because the approach is based on historical data about the causes of an illness (illness) and food damage (spoilage). The HACCP is systematic

because the HACCP concept is a detailed and thorough plan and includes operational activities step by step, procedures (procedures), and the size of the control criteria.[11–13]

The purpose of this study was to determine the characteristics of the nanoparticles of *bajakah* wood (*Spatholobus littoralis* Hassk.) and to test the anticancer activity in several cancer cell cultures, as well as to analyze the critical point of halalness of the material.

Methods

This study was a pure in vitro experimental study, with a randomized post-test only control group design. Random sampling to be included as the experimental and control groups. The allocation of research samples to the experimental group was carried out through random allocation. The research was carried out at the Indonesian Engineering Nanotechnology Laboratory and the UGM Integrated Laboratory in July–December 2020.

The subjects of this study were HTB 183 lung cancer cell culture, MCF-7 breast cancer cell culture, T47D breast cancer culture, WiDr colon cancer cell culture. In addition, we also study HeLa cervix cancer culture, HepG2 liver cancer cell culture, normal kidney cell culture. The test conducted in this study was a nanoparticle preparation of *bajakah tampala* (*Spatholobulus littoralis* Hask) from East Kalimantan, Indonesia.

Simplicia using mechanical milling provided that the milling machine is on for 15 seconds and stops for 2 minutes. It is done 40 times. Sieves the milling results using a 14 mesh (1.41 mm) sieve. Performs milling back to the sieve using wet milling with the addition of 200 mL of distilled water for every 100 grams of the sieve with the condition that it is on for 2 minutes and stops for 3 minutes 90 times. Filter the wet milling results using a 70 mesh sieve, and the nanoparticles were measured using a particle size analyzer.

The characteristic test of nanoparticles of *bajakah* wood was conducted using Beckman Coulter's particle size analyzer. The IC50 is seen by the tetrazolium 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. IC50 is a concentration that can kill 50% of cancer cells. IC50 was calculated using Probit software. The number of cancer cells was counted using a counting chamber with the dilution method. Analysis of the critical point of product halalness

is carried out by tracing the preparation process and testing the alcohol content of the preparation.

After incubation, the culture media was discarded and washed with phosphate-buffered saline (PBS), and 100 μL of MTT solution (1 mL MTT in 10 mL, culture medium) was added to each well and then incubated again at 37°C 5% CO_2 for 4 hours. After 4 hours, 100 μL SDS stopper 10% in 0.1 N HCl was added to each well (to dissolve purple formazan). Then it is stirred for 5 minutes and wrapped tightly, and left at room temperature overnight. After one night at room temperature, the absorption reading was carried out with an ELISA microplate reader at a wavelength (λ) of 595 nm.

From the results of the absorbance analysis, cell viability can be calculated using the formula life (viability)=(cb)/(ab) × 100. Letter a is the absorbance of control cells; b is the absorbance of the media control, and c is the absorbance of the sample. The cytotoxic activity of each of the doxorubicin and cisplatin test compounds was expressed by the IC50 value, which can inhibit cell growth by up to 50% calculated by probit analysis based on the relationship between levels of the inhibitor of cell growth.

This study was approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Islam Bandung, with approval number 388/Komite Etik.FK/VIII/2019.

Results

Bajakah wood is obtained from East Kalimantan, with permission from the head of the Local Office, as much as 10 kg of *bajakah* wood. The next step is to determine which *bajakah* wood will be used to determine the plant species used as the test material—taxonomy of *bajakah* plants presented in Table 1.[14]

Bajakah tampala wood preparations of simplicia are dried through winds at room temperature for seven days. After the simplicia

Table 1 Taxonomy of *Bajakah*

Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Fabales
Genus	*Spatholobus* Hassk.

Table 2 Characteristics of Nanoparticles of *Bajakah* Wood

Characteristics	Description
Temperature	25°C
Solvent	Aquadest
Reflative index	1.3328
Viscosity	0.8878 cP
Scattering intensity	11059 cps
Diameter average	176.1+/−43.7 (nm)

The first step is processing by dry mechanical milling for 15 seconds, 40 times the reinforcement; then, the results are filtered using 14 mesh. Next, the results are carried out wet milling with 200 mL for every 100 grams of the sieve result. The wet milling process is carried out for 2 minutes because there are 90 repetitions.

After wet milling, nanoparticles' nano size and characteristics were carried out using a particle size analyzer. The characteristics of *bajakah* wood nanoparticles are shown in Figure 1 and Table 2.

Measurement of the cytotoxic test of *bajakah* wood nanoparticle preparations was carried out to determine its anticancer potential against various cancer cultures. The test was carried out using

is dry, it is chopped so that the simplicia size is smaller and easy to do milling. The process of making nanoparticles is carried out in two stages.
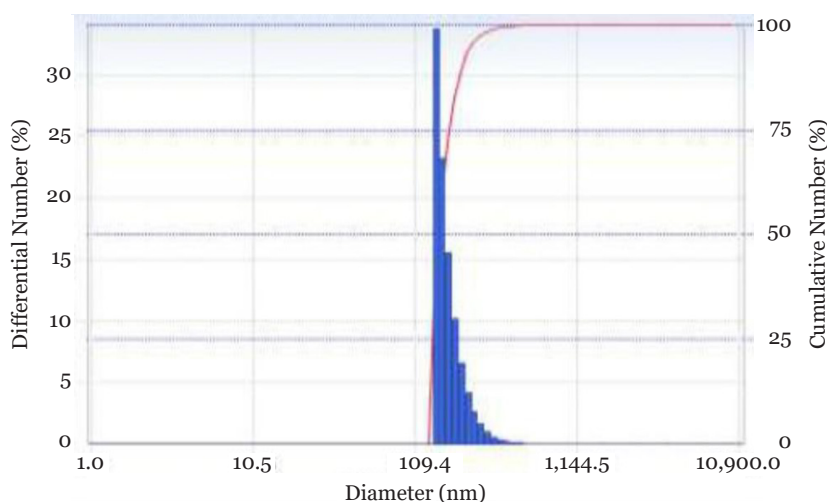
Figure 1 Characteristics of Nanoparticles of *Bajakah* Wood
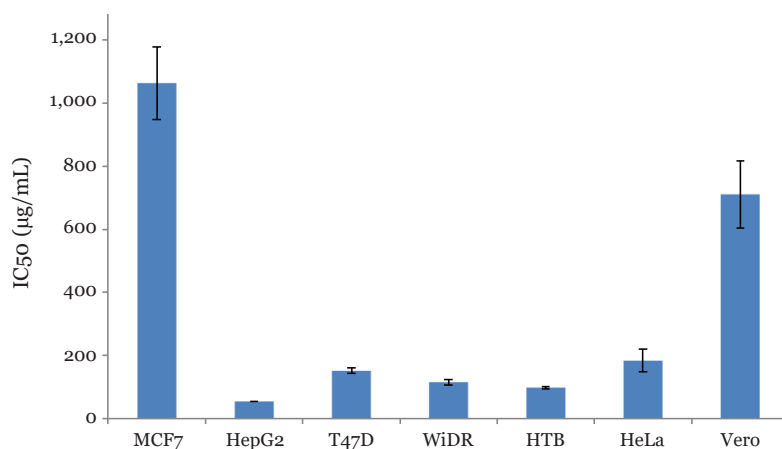
Figure 2 IC50 Bar Chart Graph of Nanoparticle of *Bajakah* Wood in Various Cancer Cell Cultures

the MTT method to obtain the concentration of compounds that could inhibit 50% of the tumor cell population (IC50). Tests were carried out at a serial concentration of 500, 250, 125, 62.5, 31.25, 15.625, and 7.8125 μg/mL. Cytotoxic test results for each compound are presented in Figure 2.

Figure 2 shows preparation I has IC50 in MCF7 cell culture of 1,063.28 (±114.98) μg/mL, IC50 in HepG2 cell culture 53.34 (±0.35) μg/mL, IC50 in T47D cell culture 150.63 (±8.44) μg/mL, IC50 for WiDR cell culture 114.38 (±7.82) μg/mL, IC50 for HTB cell culture 97.50 (±3.49) μg/mL, IC50 in HeLa cell culture 182.95 (±36.22) μg/mL, and IC50 in Vero cell culture 710.10 (±106.46) μg/mL.

Discussion

Bajakah wood, including traditional medicinal plants that inland communities of Central Kalimantan province, have empirically been used to heal some diseases. Based on previous research, this plant also contains bioactive compounds such as phenolics, flavonoids, tannins, and saponins.[15,16]

This research generally consists of 3 stages. The first stage aims to determine the characteristics of the *bajakah* wood nanoparticle preparations, where the test results show that there is only water or aqua dest in this preparation. The particle size in this preparation is 176.1+/−43.7 (nm), where the maximum size is below 250 nm, which indicates that this preparation particle is already a nanoparticle category. Nanomaterials, especially nanoparticles, are a vital component in the development of new technologies. Nanoparticle-based technology has developed in various fields, from cosmetics, medical care, medical rehabilitation, the environment to electronic technology. Nanoparticle-based materials change their physical properties with changing particle size. This phenomenon is known as the quantum confinement effect.[17,18]

In the research and development of drugs with nanoparticle preparations, or so-called nanomedicine, it is thought that they can target drugs at specific receptors. The formulation method can increase the bioavailability of herbal medicines with poor water output. The formation of nano-sized particles can coal drugs and permeability, regulate nanoparticle carriers' physicochemical properties, and increase drug absorption, distribution, and elimination in cells.[19]

The second stage of this research is to analyze the critical point of the halal nano-*bajakah* wood preparations. Some preparations often require alcohol as a suitable solvent, but alcohol is a substance or substance included in non-halal or haram. Islam has clear rules regarding the halalness of a product, including medicines. One form of the devotion of a Muslim is consuming halal and good products (*thayibah*).[20] The increasing awareness of Muslims regarding the use of halal products is a great potential and opportunity for developing halal drugs and cosmetics. As the world's Islamic cooperation organization, the Organization of Islamic Cooperation (OIC) predicts that these opportunities will continue to grow in the future. This statement is also supported by an increase in the market share of halal medicines and health products in Indonesia.[21] One of the many herbal medicines developed in Indonesia is an anticancer drug.

Stage 3 aims to see the anticancer effect of *bajakah* wood preparations on various cancer cell cultures. In developing new anticancer drugs as candidates for cancer therapy agents, preclinical testing is crucial to determine its potential cytotoxic activity. The cytotoxic test is used as an early-stage screening to determine the effect of a natural substance in inhibiting tumor cell growth. A compound is considered to have anticancer properties if it can inhibit 50% of the tumor cell population at a specific concentration. The requirements that must be met for a cytotoxicity test system include that the test system can produce a reproducible dose-response curve with low variability. The response criteria must show a linear relationship with the number of cells, and the information obtained from the dose-response curve must be in line with the effect that appears. One of the commonly used methods for determining cell counts is the MTT method.[22,23]

In this study, the cytotoxic test results of *bajakah* wood nanoparticle preparations against MCF7 cell culture of 1,063.28 (±114.98) μg/mL were classified as having no anticancer effect. IC50 in HepG2 cell culture 53.34 (±0.35) μg/mL, classified as moderate anticancer, IC50 in T47D cell culture 150.63 (±8.44) μg/mL. IC50 in WiDR cell culture 114.38 (±7.82) μg/mL including weak category, IC50 in HTB cell culture 97.50 (±3.49) μg/mL were included in the medium category. In contrast, IC50 in HeLa cell culture 182.95 (±36.22) μg/mL were included in the

weak category. IC50 in Vero cell culture 710.10 (±106.46) µg/mL, showing *bajakah* wood nano preparations are not toxic to normal cells.[24,25]

Bajakah tampala contains flavonoids, alkaloids, tannins, and phenolic acids, which have anticancer effects. The critical mechanism of flavonoids is to prevent the metabolic activation of carcinogens through phase I metabolic enzymes (cytochrome P450). It can metabolically activate most of the procarcinogens that can trigger carcinogenesis. These flavonoid compounds work by inhibiting the activity of specific P450 isozymes, such as CYP1A1 and CYP1A2, so they have a protective role against induction of cell damage by carcinogen activation.[26]

Alkaloids and phenolic acids can inhibit cell proliferation processes, stimulate apoptosis, and inhibit the formation of new blood vessels (angiogenesis).[26–28] Phenolic acid is a material that has bioactivities such as high antioxidants.[29] Alkaloids also can inhibit cell survival, proliferation, invasion, and angiogenesis in human glioma cells. In addition, it can induce HeLa cervical cell death with apoptosis and necrosis.[29]

Conclusions

This study concludes that pirated wood nanoparticles are not critical in terms of halal ingredients. At the same time, their anticancer activity is weak against breast cancer and uterine cervical cancer, categories against liver cancer and lung cancer, while it is not toxic to normal cells.

Conflict of Interest

There was not a conflict of interest in this article.

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RESEARCH ARTICLE

Effect of Health Counseling about IUD to Knowledge and Attitude on Married Couple in Serang Regency

Suraya Mansur,[1] Dewi Hartaningrum,[1] Titi Legiati[2]

[1]Department of Communication Science,
Faculty of Communication Science, Universitas Mercu Buana, Jakarta, Indonesia,
[2]Department of Midwifery, Politeknik Kesehatan Kementerian Kesehatan Bandung, Bandung, Indonesia

Abstract

Health counseling about contraception is essential to provide more knowledge about how to use contraception and improve the attitude and behavior of the family toward the Family Planning Program. This study aimed to determine the effect of counseling on the intrauterine device (IUD) knowledge and attitudes. This research was conducted in Bojong Menteng village, Tunjung Teja district, Serang regency, in February–July 2019. This study used the true experimental design method to look for the treatment effect on others in controlled conditions using pretest-posttest control group design and a quantitative research approach. In this study, the experimental and the control group are given a pretest to find out the initial conditions to see whether there are differences between the experimental group and the control group. Samples used random sampling techniques where 40 people were divided into two groups who have not used the IUD and have two children and more. The study employed paired t test and unpaired t test to analyze the data. The results showed that the average knowledge of the experiment group increased to 72, and the average knowledge of the control group increased to 70.2. In addition, the average attitude of the experiment group increased to 82.35. The difference between the two groups was only seen in wearing, where the experimental group showed positive behavior towards using the IUD. The conclusion is that counseling through leaflets, information education counseling kit, and direct explanation have positive responses.

Keywords: Attitudes, counseling, health communication, IUD, knowledge

Efek Penyuluhan Kesehatan mengenai IUD terhadap Pengetahuan dan Sikap pada Pasangan di Kabupaten Serang

Abstrak

Penyuluhan kesehatan tentang kontrasepsi penting dilakukan untuk memberikan lebih banyak pengetahuan tentang cara penggunaan kontrasepsi serta meningkatkan sikap dan perilaku keluarga terhadap Program Keluarga Berencana. Penelitian ini bertujuan mengetahui pengaruh penyuluhan tentang alat kontrasepsi dalam rahim (AKDR) terhadap pengetahuan dan sikap. Penelitian ini dilaksanakan di Desa Bojong Menteng, Kecamatan Tunjung Teja, Kabupaten Serang pada Februari–Juli 2019. Metode yang digunakan *true experimental design* dengan menggunakan *pretest-posttest control group design* dan pendekatan kuantitatif untuk mencari pengaruh perlakuan terhadap yang lain dalam kondisi yang terkendalikan. Dalam penelitian ini kelompok eksperimen dan kelompok kontrol diberi *pretest* untuk mengetahui keadaan awal adakah perbedaan antara kelompok eksperimen dan kelompok kontrol. Sampel menggunakan teknik *random sampling* berjumlah 40 orang dibagi dalam dua kelompok yang belum menggunakan AKDR dan mempunyai dua anak dan lebih. Data dianalisis dengan uji t berpasangan dan uji t tidak berpasangan. Hasil penelitian menunjukkan bahwa rerata pengetahuan kelompok eksperimen meningkat menjadi 72, sedangkan rerata pengetahuan kelompok kontrol meningkat menjadi 70,2. Selain itu, rerata sikap kelompok eksperimen meningkat menjadi 82,35. Perbedaan kedua kelompok tersebut hanya terlihat pada perilaku memakai saja bahwa kelompok eksperimen menunjukkan perilaku positif terhadap pemakaian AKDR. Hal tersebut menunjukkan bahwa penyuluhan melalui *leaflet*, kit konseling pendidikan informasi, dan penjelasan langsung memiliki respons positif.

Kata kunci: AKDR, komunikasi kesehatan, pengetahuan, penyuluhan, sikap

Introduction

Health communication is one of the essential efforts in limiting the number of populations. Family planning programs and reproductive health become the main issues to be discussed in health communication as they significantly impact family quality. The decision to use contraception should have overcome the population issue. The local government has authority and flexibility in problem formulation and policymaking to reduce the number of populations. On the other hand, society needs to receive accurate information and understanding of contraception. Information on contraception is prominent in measuring the success of the family planning program.[1] The policy to support Family Planning Program should be improved, especially the communication skill of the counselor in providing Family Planning counseling.[2]

Many fertile married couples do not understand the benefit of IUD with the long-acting contraception method (LACM) and how contraception has fewer side effects than other contraceptions do. Around 96% of Indonesian women only know pill and injected contraceptives, also known as non-LACMs, while only 73.8% know about the intrauterine device (IUD) as contraception.[1]

Human behavior could change if there is a stimulus. The stimulus could be in the form of counseling or information related to the behavior. For example, if someone who does not use contraception could change her mind to use contraception because of the counseling or other program. This study aims to analyze the effect of health counseling about intrauterine device (IUD) on the knowledge and attitude of the fertile married couple.

Methods

The researcher in this study created leaflets independently and conducted two groups experiment study on the effect of counseling by leaflet or leaflet followed by an explanation. Thus, according to the elaboration above, the research question of this study is how does health counseling about IUD affect the knowledge and attitude of fertile married couples in Bojong Menteng village, Tunjung Teja district, Serang regency?

This study used the S-O-R theory, which considers attitude change as similar to the learning process. In examining attitude, three essential variables support the learning process, attention, understanding, and acceptance. The message in this theory became the stimulus. The organism is individual or communicant. Furthermore, a response is reaction, perception, affect, or consequence; thus, this theory's response element is the effect.[3–6] The change in attitude happened when the communicant has the willingness to use IUD based on the counseling that has been given.

As Rogers[7] stated, this study is also related to health communication: "health communication has been defined as referring to any human communication whose content is concerned with health." A study on communication health was conducted by Thomas,[8] Rice and Atkin[9] on public health, Abroms and Lefebvre[10] on health campaign by Obama, health campaign,[11] and health campaign through social marketing.[12]

This study used the true experiment design method. The method is employed to determine the effect of specific treatment toward others in a controlled condition, where this study is a quantitative research method.[13] In addition, this study used a pretest-posttest control group design. Two groups in this design are selected randomly and given a pretest to determine the initial condition whether there is a difference between the experiment group and the control group.[13]

The variables of this study are independent variables and dependent variables. Independent variables are counseling by leaflet and information education counseling/*komunikasi, informasi, dan edukasi* (KIE) kit, while dependent variables are knowledge and attitude of fertile married couples toward IUD. The population is 562 fertile married couples in Bojong Menteng village, Tunjung Teja district, Serang regency.

This study used simple random sampling in collecting the sample by choosing 40 respondents randomly from 562 fertile married couples that are registered as Family Planning participants and have not used IUD in Bojong Menteng village, Tunjung Teja district, Serang regency with the criteria as follows: fertile married couple that with two or more children, fertile married couples that have not used IUD, fertile married couples who can read and write, and willing to be involved.

The respondents joined the counseling, and the media used is a leaflet and KIE kit. The information given is the definition of IUD, its

procedure, side effects, benefit, contraindication, induction time, and essential things to be considered after the induction.

The researcher collected primary data through attitude and knowledge questionnaires. The data were taken twice on the same group, which is pretest and posttest data. The steps of collecting data are: Step 1: (1) the researcher explained the aim and procedure of the research to the respondents, then asked for their agreement and

Figure 1   IUD Leaflet

Figure 2   KIE Kit

signature on the informed consent provided; (2) the researcher divided respondents into two groups with 20 individuals each; (3) the respondents filled attitude and knowledge on the IUD questionnaire before the treatment was applied; (4) after filling the questionnaire (pretest), the treatment/experiment group (Group 1) joined counseling with leaflet, KIE kit, and explanation for an hour; (5) meanwhile, the control group (Group 2) was given a leaflet without explanation after filling the questionnaire (pretest); (6) all respondents went home and are reminded to be back a week later.

Step II: similar to Step I. Step III: after two counseling sessions, respondents filled the attitude and knowledge of the IUD questionnaire (posttest). Step IV: after the pretest, treatment, and posttest, the researcher observed the respondents' attitudes toward IUD for months to determine whether the respondents are willing to use IUD or not.

This study used a t test sample related/paired in analyzing the data to determine the changes in respondents' knowledge, attitude, and behavior.

The validity test result from the questionnaire is the coefficient of 0.05, r table of 0.361, total correlation >0.361, and positive, then the statement is valid. However, if the statement is not valid, it would be terminated.

A variable is reliable when the Cronbach's alpha value is >0.60. In this study, Cronbach's alpha value for the knowledge variable is 0.924, and the attitude variable is 0.724, respectively.
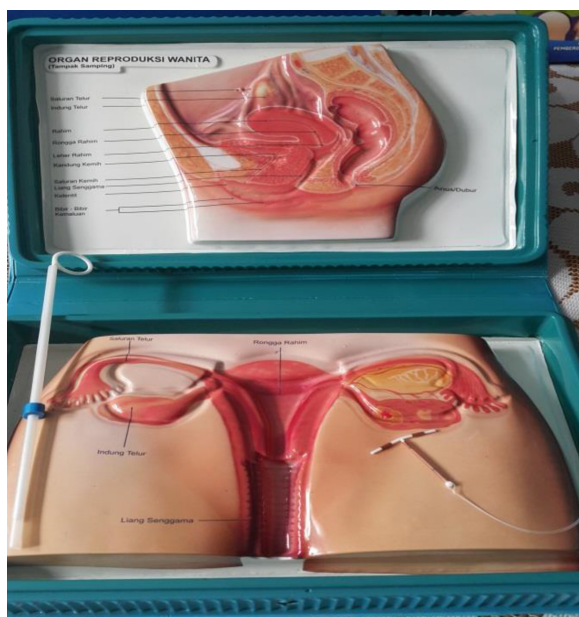
Results

Most of the respondents are elementary and high school graduates. Eight respondents are elementary school graduates (40%) in the control group, and eight are high school graduates (40%). Meanwhile, seven respondents are elementary school graduates (35%) in the intervention group, and seven others are high school graduates (35%). Most of the respondents have 1–2 children (13 respondents (65%) in the experiment group and 12 respondents (60%) in the control group). Most of the respondents used contraceptive injection as 12 respondents (60%) of the experiment group and ten respondents (50%) of the control group used contraceptive injection. Most of the respondents are not working, as 18 respondents (90%) of the experiment group and 20 respondents (100%) of the control group are unemployed. Husbands of the respondents of both groups are primarily

Table 1 Paired T Test the Effect of Health Counseling about IUD through Leaflet and KIE Kit on the Knowledge of Experiment Group

Variables	n	Average ±	Average Difference ≠	95% CI	p
Knowledge					
Pre-treatment	20	65.80±9.49	6.20±11.34	0.88–11.51	0.024
Post-treatment	20	72.00±12.31			
Attitude					
Pre-treatment	20	76.65±6.99	5.70±10.72	0.68–10.71	0.028
Post-treatment	20	82.35±11.83			

Table 2 Paired T Test the Effect of Health Counseling about IUD through Leaflet on the Knowledge of Control Group

Variables	n	Average ±	Average Difference ≠	95% CI	p
Knowledge					
Pre-treatment	20	60.60±8.63	9.60±9.57	5.12–14.08	0.000
Post-treatment	20	82.35±11.83			
Attitude					
Pre-treatment	20	74.07±9.59	5.41±10.70	0.40–10.42	0.036
Post-treatment	20	79.48±10.57			

working (90% of the experiment group and 100% of the control group).

Table 1 shows the p value of the statistic test was 0.024, which means alpha 5%, and there was a significant difference in the average knowledge of the experiment group during the intervention. On the other hand, the p value of the statistic test is 0.028, which means alpha 5%, and there is a significant difference in the average attitude of the experiment group during the intervention.

The average knowledge of the experiment group before the counseling and intervention was 65.8, but the number increased to 72 after counseling and intervention using leaflet, explanation, and KIE kit. On the other hand, the

average knowledge of the control group before the counseling was 60.6, and the number also increased to 70.2 after counseling using a leaflet.

Table 2 shows the p value of the statistic test was 0.000, which means that there was a significant difference in the average knowledge of the control group during the counseling. On the other hand, the p value of the statistic test was 0.036, which means that there was a significant difference in the average attitude of the control group during the counseling.

The average attitude of the experiment group before the counseling and intervention was 76.65, but the number increased to 82.35 after counseling and intervention using leaflet,

Table 3 Unpaired T Test the Counseling Effectiveness on the Knowledge on IUD

Variables	n	Average ±	Average Difference 95% CI	p
Knowledge				
Experiment group	20	6.20±11.34	3.40 (3.32–10.12)	0.033
Control group	20	9.60±9.57		
Attitude				
Experiment group	20	5.45±10.73	0.05 (0.92–6.82)	0.835
Control group	20	5.40±10.75		

Table 4 Respondents' Behavior on IUD Usage

| Treatment | IUD Usage | | p |
| | Not Use | Use | |
	n=36	n=4	
Control	20	0	0.035
Experiment	16	4	

explanation, and KIE kit. Meanwhile, the average attitude of the control group before counseling was 74.1, and the number also increased to 79.35 after counseling using leaflets.

Table 3 shows no significant differences between the average knowledge of the experiment and the control group (p=0.33). However, the average knowledge of the control group (9.60) was higher than the average knowledge of the intervention group (6.20). As well, no significant differences between the average attitude of the experiment and the control group (p=0.835). However, the average attitude of the experiment group (5.45) was higher than the average knowledge of the control group (5.40).

Thus, despite the difference, both groups showed improvement in knowledge and attitude. An observation was conducted to determine the respondents' behavior toward IUD.

Table 4 showed that there was an effect of counseling on the usage of IUD. The counseling using leaflet, explanation, and KIE kit has led 4 of 20 people in the experiment group to use IUD. Meanwhile, none of the control group respondents used IUD after counseling, only using a leaflet. The data implied that using the KIE kit effectively changed the respondents' behavior as they became more enthusiastic compared to other methods.

Discussion

A study about knowledge on IUD was conducted by Destyowati,[14] the increase of IUD usage in the US,[15] population control strategy using IUD.[16]

The long-acting contraception method (LACM) is effective contraception because its failure rate is only 0.58−0.78%. IUD is immediately effective after being inducted, and it is effective in the long term until ten years for CuT-380A. However, acceptors still do not perceive IUD as the primary contraception choice because the acceptors do not understand the benefit. The information that is not complete and effective given by the contraception service officer is the main reason for the lack of understanding of IUD. On the other hand, the cultural aspect also influences the use of IUD. Several women do not want to use IUDs because they are ashamed of their husbands and will not use them.[17] The rumors about IUD failure also create fear and discomfort to use IUD.

Health counseling about contraception is essential to provide more knowledge about how to use contraception and improve the attitude and behavior of the family toward the Family Planning Program. The counseling ideally could improve the knowledge about Family Planning Program and its services. Furthermore, understanding and positive reactions from the society on Family Planning Program are expected to improve the nation's prosperity.

Several studies on the effectiveness of health counseling showed that it could improve society's knowledge, attitude, and behavior on the use of IUD to control the birth rate in Indonesia and other countries.[15,16,18−20]

Serang regency is an area that includes 29 districts. Its population is composed of 742,298 males and 720,296 females. The citizens are generally aware of contraception, and they have been using contraception with various methods and choices. It shows that most citizens are open-minded and willing to support the government's program in controlling the birth rate. However, according to the Women Empowerment and Family Planning Agency of Serang regency data, most citizens prefer to use short-term contraception such as pills and injections. The data also reported that in Bojong Menteng village, Tunjung Teja district, only 15 of 562 married couples use IUD.[21]

The previous study found that the low rate of IUD usage in Bojong Menteng village is caused by the lack of information that allows negative rumors about IUD to spread widely. Furthermore, counseling provided by the counselor is not exciting and persuasive enough, although IUD induction service is provided in health centers.[21] In addition, information about IUD is not entirely written in the leaflet created by Women Empowerment and Family Planning Agency.

This health campaign is conducted through counseling. Counseling aims to change the behavior, attitude, and knowledge of the communicants so that they are willing to

apply the innovation provided to improve the life quality of family and society. Thus, every counselor would understand the factors related to the communicant's motivation in joining the counseling.

Counseling as a learning process is one of the ways to persuade society to be more active during the learning process. The learning process itself is a process of delivering responses toward every stimulation received during the learning process. Thus, every counselor needs to understand the stimulus-response theory that someone will respond to the stimulus received. The clarity in communication is determined by four elements: source, message, channel, and communicant.[22–25]

Human receives knowledge through experiences. Knowledge is the result of a human's senses, or someone's understanding of an object through senses (eyes, nose, ears, and others). The process of gaining knowledge is influenced by the intensity of attention and perception toward a specific object. Most of the knowledge is gained through ears and eyes. Every individual's knowledge has a different intensity or level. The level is generally divided into six levels of knowledge: (1) know, (2) comprehension, (3) application, (5) synthesis, and (6) evaluation.[26]

Attitude is the response toward stimulus or particular objects involving argumentation and emotions (happy-not happy, agree-disagree). Attitude is a syndrome or a collection of indications in responding to a stimulus or object. Thus, attitude involves thinking, feeling, attention, and other psychological indications.[27,28] Knowledge, thinking, belief, and emotion are essential in deciding attitude. The level of attitude is varies depending on the intensity, such as (1) receiving, (2) responding, (3) valuing, and (4) responsible.[26] Behavior is the activity of an individual that includes walking, talking, crying, laughing, working, studying, writing, reading, etc. Based on the form of the response toward the stimulus, the behavior could be divided into two: (1) covert behavior and (2) overt behavior.[26]

Knowledge is the result of a learning process where an individual sensing a specific object—sensing through human senses such as sight, hearing, smell, taste, and touch. Most of the human's knowledge is gained through sight and hearing.[26] Knowledge of cognition is an essential domain of behavior forming (overt behaviour).

According to the constructivist approach, knowledge is dissimilar to a studied truth—however, cognitive construction of an individual towards an object, experience, and environment. Therefore, knowledge is not an available material that people can utilize anytime they need it. Instead, it is a systematic forming process that will experience changes along with new understandings. Furthermore, counseling through the leaflet and KIE kit as communication, information, and education media is essential in deciding IUD as a contraception method. It provides reference/technical information on IUD and breaks the stereotype that raises concerns about IUD.

Two factors influence knowledge: (1) education and (2) mass media/information.[29,30] In the experiment group, respondents received an interesting and informative leaflet and a presentation on using IUD through the KIE kit. The respondents of the experiment group showed enthusiasm when the KIE kit was presented and explained. The enthusiasm can also be perceived through the average increase in statistic calculation.

According to S-O-R theory on counseling, stimulus in the form of a message about IUD has been tested. Response or reaction toward the message will result in an agreement or vice versa. Thus, the theory assumed that certain verbal words, signs, non-verbal, and symbols would stimulate others to respond in specific ways.

The experiment group in this study showed that information media through the leaflet and KIE kit with direct explanation positively impact the change in knowledge and attitude, shown by the increase in average knowledge and attitude after the experiment.

Meanwhile, the respondents of the control group were counseled only through leaflets as the media. The leaflet received is the same as the one that the experimental group also received. It has understandable information with an interesting design. Although the counseling was conducted by only distributing leaflets, the counseling has a positive impact on the control group and the experiment group. It was shown by the increase in average knowledge and attitude after the experiment on the control group. The finding indicates that the leaflet could provide enough information about IUD to the respondents.

The findings are in line with the research conducted by Antini and Trisnawati[31] on choosing contraception, Zuhriyah et al.[32] on Family Planning village, Farrar et al.[20] on the

importance of contraception, Yoo et al.[33] on health communication, and health campaign.[34]

Conclusion

The counseling through leaflets, information education counseling kit, and direct explanation have positive responses.

Conflict of Interest

There was not a conflict of interest in this article.

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RESEARCH ARTICLE

Depression Leads to Physical Inactivity in Patients with Beta-Thalassemia Major

Faza Nurul Wardhani,[1] Susanti Dharmmika,[2] Hilmi Sulaiman Rathomi[3]
[1]Medical Undergraduate Study Program, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[2]Department of Medical Rehabilitation, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[3]Department of Public Health, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

Beta-thalassemia major (BTM) is difficult to treat chronic disease, causing physical and psychological burdens for the patient. Several studies have confirmed a decrease in physical activity and depression in thalassemia patients, but limited studies examine the relationship between these two conditions. This study aims to analyze the relationship between depression and physical activity in BTM patients in Bandung city. It was analytical observational research with a cross-sectional design. Data were collected during September–December 2018 by interviewing 65 patients selected by simple random sampling from 300 thalassemia patients registered at the Association of Parents with Thalassemia Indonesia/*Perhimpunan Orangtua Penderita Thalassemia Indonesia* (POPTI) Bandung city. The instruments used were the Global Physical Activity Questionnaire (GPAQ) to measure physical activity and the Beck Depression Inventory (BDI) to assess depressive symptoms. Data were analyzed by chi-square test using SPSS for Windows ver. 23.0. The results showed that most BTM patients in Bandung city were depressed (52%) and had low physical activity levels (65%). Furthermore, there was a statistically significant relationship between depression and physical activity in thalassemia patients in Bandung city (p=0.04, p<0.05). Therefore, it can be concluded that BTM patients in Bandung city with depression have lower physical activity.

Keywords: BDI, beta-thalassemia major, depression, GPAQ, physical activity

Depresi Berdampak pada Aktivitas Fisik yang Rendah pada Pasien Talasemia Beta Mayor

Abstrak

Talasemia beta mayor merupakan penyakit kronis yang sulit disembuhkan sehingga menimbulkan beban fisik dan psikologis bagi pasien. Beberapa penelitian telah mengonfirmasi penurunan aktivitas fisik dan depresi pada pasien talasemia, namun studi yang mengkaji hubungan antara kedua kondisi ini masih terbatas jumlahnya. Penelitian ini bertujuan menganalisis hubungan antara kondisi depresi dan tingkat aktivitas fisik pada penderita talasemia beta mayor di Kota Bandung. Desain penelitian bersifat observasional analitik dengan rancangan potong lintang. Pengambilan data dilakukan selama September–Desember 2018 dengan mewawancarai 65 pasien yang dipilih secara *simple random sampling* dari 300 pasien talasemia yang terdaftar di Perhimpunan Orangtua Penderita *Thalassemia* Indonesia (POPTI) Kota Bandung. Instrumen yang digunakan adalah *Global Physical Activity Questionnaire* (GPAQ) untuk mengukur aktivitas fisik dan *Beck Depression Inventory* (BDI) untuk menilai gejala depresi. Data dianalisis dengan uji *chi-square* menggunakan *SPSS for Windows ver. 23.0*. Hasil penelitian menunjukkan mayoritas penderita talasemia beta mayor di Kota Bandung mengalami depresi (52%) dan memiliki tingkat aktivitas fisik rendah (65%). Selanjutnya, terdapat hubungan bermakna secara statistik antara depresi dan aktivitas fisik pada penderita talasemia di Kota Bandung (p=0,04; p<0,05). Oleh karena itu, dapat disimpulkan bahwa penderita talasemia beta mayor di Kota Bandung yang mengalami depresi memiliki aktivitas fisik yang lebih rendah.

Kata kunci: Aktivitas fisik, BDI, depresi, GPAQ, talasemia beta mayor

Introduction

Thalassemia is the most common genetic blood disease globally, characterized by defects in hemoglobin production and red blood cell destruction. Beta-thalassemia major (BTM) is the most severe form of thalassemia in which severe hemolytic anemia occurs.[1] In 2011, there were 5,501 thalassemia patients in Indonesia, of which 800 or about 15% came from West Java. The prevalence of BTM in Bandung region, West Java, was 800, while Bandung city itself was 300.[2] Thalassemia is a chronic high-cost disease that can be a stressor for patients in socioeconomic, psychosocial, and disease burden. Uncertainty about the future, worry of being a family burden, long-term complications of the illness, discrimination by friends or coworkers, and fear of being stigmatized by society make thalassemia sufferers a trigger for depression.[3]

Depression generally occurs in people with unhealthy behavior and people with chronic diseases, including beta-thalassemia major.[4] Similar to other people, patients with chronic illness could suffer depression due to stress, disease burden, hereditary, and socioeconomic stress such as high medical expenses and fear of losing a job, but with a higher risk. Several studies state that the prevalence of depression in thalassemia patients is >30%,[5,6] and thalassemia patients have a 4–5 fold risk of developing depression than average adults.[7–9]

Symptoms of thalassemia are similar to those of anemia, characterized by weakness, fatigue, lethargy, and fatigue. As a result, it can reduce work productivity and physical activity.[10] Both pediatric and adult thalassemia sufferers spend more time with a sedentary lifestyle per day than their age group.[11] Thalassemia sufferers with depression experience decreased quality of life and almost two times the risk of limiting physical activity when compared to patients without depression.[3] Research conducted by Gariépy et al.[11] stated that only 12.5% of thalassemia patients performed moderate and vigorous activity following the recommendations of the Physical Activity Guidelines.

Beta-thalassemia major is a chronic disease that is difficult to cure, resulting in an increased disease burden. It can increase the risk of developing depression. Thalassemia patients with depression may experience limited physical activity. Various studies have been conducted to describe depression and physical activity levels in beta-thalassemia major patients.[12–14] However, there is limited research examine the relationship between depression and the level of physical activity, even though depression and physical activity are factors that affect the quality of life in beta-thalassemia major patients.[12] This study aims to analyze the relationship between depression and the level of physical activity in beta-thalassemia major sufferers in Bandung city.

Methods

The subjects of this research were BTM patients registered in the Association of Parents with Thalassemia Indonesia/*Perhimpunan Orangtua Penderita* Thalassemia Indonesia (POPTI) Bandung city, which have 300 members. The number of subjects that meet the inclusion criteria is 200. The minimum sample size from the calculation with the formula of proportion difference was 46. We selected the subject using a simple random sampling method with a random number generator from Microsoft Excel. We added some other subjects to anticipate the dropout, and we got 65 patients in total.

The inclusion criteria include patients aged ≥ten years who are registered at POPTI Bandung city, have regular blood transfusions at least once a month during 2018, and are willing to participate in research. The exclusion criteria included beta-thalassemia major patients with other hypertension, diabetes mellitus, and congenital heart disease.

An observational analytic study with a cross-sectional design determined the relationship between depression and physical activity levels as assessed using the Beck Depression Inventory (BDI) with the Global Physical Activity Questionnaire (GPAQ).

The BDI contains a depression scale consisting of 21 questions that can evaluate symptoms of depression. Each question has values ranges from 1–4, and the scores of each question are added up to get a total score. The results were classified into normal if the patient has a total score of less than nine and depression if more than that. We chose the BDI as an instrument because this questionnaire is easy to use in patients with diverse characteristics like in this study, easier to categorize, and able to measure depression, which makes analysis easier. The GPAQ consists of 16 questions that are grouped to capture physical

activity in three behavioral domains, namely physical activity on weekdays, trips to and from places of activity, and recreational activities. The GPAQ measurement results are classified into low and medium-high.

The data was collected from September–December 2018. Data analysis was performed using the SPSS for Windows version 23.0 at 95% confidence level and p value≤0.05. This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Islam Bandung number: 65/Komite Etik.FK/III/2018.

Results

Table 1 shows that more male respondents (52%) with an age median are 12 years, ranging from 10–17 years. Based on the residence, most respondents live in Bandung city (38 respondents, 58%), and most are still in elementary school (66%). There is one respondent who does not go to school. From the socioeconomic aspect, most of their parents are in low social-economic status with a salary below the regional minimum wage of Bandung city in 2018, consisting of 60 respondents (92%).

Based on the health status, we can see that most respondents were diagnosed with thalassemia at 0–2 years. As many as 58 respondents (89%) and 60 respondents (92%) had blood transfusions 1–2 times/month.

Table 2 shows the most of the beta-thalassemia major sufferers in Bandung experienced depression (52%) and do low-level physical activity (65%). Among this 52% of patients with depression, the severity is ranging from mild to severe symptoms.

The proportion of depressive symptoms based on the components of the BDI questionnaire shows that the most prominent depressive symptoms in patients with BTM in Bandung are fatigue (constantly feeling tired), sadness, feeling guilty, crying easily, and irritability (Table 3). There is also a small number of patients who have severe symptoms such as suicidal ideation (14%).

In Table 4, the p value is 0.04 (p<0.05) using the chi-square test, so it can be concluding there is a statistically significant relationship between depression and the level of physical activity. In addition, the majority of respondents who experienced depression have a low level of physical activity.

Discussion

In this study, 52% of respondents were male. It is consistent with the epidemiology of BTM and various previous studies such as by Yahia et al.,[6] with 58.1% of his respondents were male. In a

Table 1 Respondents' Characteristics

Categories	f (n=65)	%
Sex		
Male	34	52
Female	31	48
Age		
Median (min–max)	12 (10–17)	
Residence		
West Bandung	9	14
Bandung regency	11	17
Bandung city	38	58
Cimahi	7	11
Education		
No school	1	2
Elementary school	43	66
Junior high school	17	26
Senior high school	4	6
Occupation		
No school	1	1
Student	64	99
Parents' monthly income (IDR)		
<3,091,345.56 (minimum wage)	60	92
>3,091,345.56	5	8
Age at diagnosis (years)		
0–2	58	89
>2	7	11
Transfusion frequency		
1–2 times/month	60	92
More than twice/month	5	8

Table 2 Depression and Physical Activity Level of Patients

Category	n=65 (%)
Depression	
Yes	34 (52)
No	31 (48)
Physical activity	
Low	42 (65)
Moderate–high	23 (35)

Table 3 Proportion of Depression Symptoms in Patients based on Beck Depression Inventory

BDI Component	f (n=65)	%
Fatigue	39	60
Sadness	38	58
Feeling guilty	34	52
Crying	32	49
Irritability	32	49
Sleep disturbed	31	48
Worried about health	30	46
Feeling punished	29	45
Dissatisfaction	27	42
Anorexia	25	38
Look unattractive	23	35
Feeling a failure	22	34
Difficulty with decisions	22	34
Dissapointed in self	21	32
Critical of self	18	28
Discouraged	17	26
Work inhibition	17	26
Weight loss	14	22
Discouraged about future	13	20
Loss of interest in people	13	20
Suicidal ideation	9	14

similar study, the number of BTM sufferers was more male than female (52–63%).[1,15,16] Another characteristic of respondents in this study also resembling some previous studies, such as their age, occupation, education, and socioeconomic level.[1,16–18]

Most of the respondents were diagnosed with thalassemia at the age of 0–2 years, as many as 58 respondents (89%). Similar to a study conducted by Fibach and Rachmilewitz,[19] most people with BTM were diagnosed within the first two years of life. Most of the respondents in this study had blood transfusions 1–2 times/month, and this was a little less frequent than some findings in

another study that mentioned that the majority of BTM patients had blood transfusions every 3–4 weeks.[1,20]

Most of the BTM sufferers in Bandung were depressed (34 respondents, 52%). This is slightly higher but still in line with some previous research such as Pattanashetti et al.[12] (49.4%). Several similar studies state which the prevalence of depression in thalassemia patients is >30%.[5,6] The high rate of depression is thought to be due to the many risk factors present in the patients, such as socioeconomic and psychological stress, both personally and in families.

In this study, the most prominent symptoms of depression in patients with BTN in Bandung were fatigue, sadness, feeling guilty, crying easily, and irritability. The results of a similar study stated that as many as 85% experienced a depressive mood, 81% were easily tired, 62.7% were irritable, and 50% felt punished.[21–23] A study conducted by Kumar et al.[24] showed that the prevalence of depressive mood symptoms and irritability was more common in thalassemia sufferers.

Most BTM sufferers in Bandung did the low physical activity, as many as 42 respondents (65%). Jatnika's[14] research supported the results of this study, it was found that 35 respondents (56%) had a low level of physical activity in PMI Hospital Bogor city. This is in line with a similar study that states that thalassemia sufferers have a lower activity level than children their age. There is no significant difference in the physical activity performed pre-transfusion and post-transfusion.[11] This can be caused by depression,[25] low levels of Hb in the long term,[26] the buildup of iron due to repeated blood transfusions and not taking iron-chelating drugs,[27] and pain resulting from bone marrow expansion and loss of bone mass.[28] Many factors can make BTM patients more susceptible to depression and low physical activity, including the impact of therapy and transfusions. The adverse side effects of

Table 4 Association of Depression and Physical Activity Level in Beta-Thalassemia Major Patients

Depression	Physical Activity Level				Total		p
	Low		Moderate–High				
	n=42	%	n=23	%	n=65	%	
Yes	26	76	8	24	34	100	0.04[*]
No	16	52	15	48	31	100	

Note: [*]chi-square test, p<0.05 significant

transfusions are often the result of low adherence to iron-chelating drugs.[29]

The results of statistical tests using the chi-square test at the 95% degree of confidence showed a statistically significant relationship between depression and the level of physical activity in patients with BTM with a p=0.04 (p<0.05). The majority of respondents experienced depression with a low level of physical activity as many as 26 people (76%). This association was in line with research by Karacan et al.,[30] which shows a relationship between high depression and decreased quality of life, especially physical activity. Several similar studies suggest that physical activity is significantly affected by depression in people with beta-thalassemia major.[9,13,31] Research conducted by Mutlu et al.[32] has a different result, which shows that there is no significant relationship between depression and physical activity in patients with other chronic diseases, namely, type 1 diabetes. The different research results can be caused by differences in the research instruments used, namely the Children's Depression Inventory (CDI) which measures depression symptoms more than the BDI; and most of the items measure cognitive aspects compared to somatic aspects and behavioral.[33]

During the first year of life, the child cannot comprehend the beta-thalassemia major disease comprehensively. As they enter their teens, children become more aware of the clinical manifestations of beta-thalassemia major. Thalassemia sufferers are aware of differences between themselves and children of their healthy age, primarily related to physical appearance (facial, stunted growth, bone deformity) or the inability to do physical activity. They develop a sense of resistance to disease, insecurity, and prolonged sadness that can be become a trigger for depression.[3]

Beta-thalassemia major patients with depression have the possibility of experiencing limited physical activity due to depression and the biological changes they suffer due to their diseases. Depressive symptoms can cause significant disruption to daily physical activities. This symptom indirectly becomes an additional burden for BTM patients. The patients who experience depression are often associated with an increased disease burden in the form of pain and fatigue, and additional functional disorders that can result in decreased physical activity.[25]

This study highlights the need for comprehensive care for patients with thalassemia to have a good quality of life, not just treatment for the disease itself. To improve the patients' quality of life, it is essential to initially address one of the more easily modified physical activity or depression prevention conditions. This support can be done by family members as caregivers or health workers as well. Unfortunately, in this study, we did not measure several aspects that can separately affect the onset of depression and decrease physical activity levels. These include biological factors such as calorie intake, hemoglobin levels, family support, and the patient's environmental conditions. The absence of some of these data is a limitation of this research that should be considered in future studies.

Conclusions

Although depression and physical inactivity can occur separately in BTM patients, there is an association between these two conditions. Therefore, BTM patients who have depression will tend to have a low level of physical activity.

Conflict of Interest

The authors have no conflict of interest with any patients or institutions in this research.

Acknowledgments

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RESEARCH ARTICLE

Effect of Labor Camera on the Duration of the Second Stage Labor in Primipara

Yetti Purnama, Kurnia Dewiani, Linda Yusanti

Department of Midwifery, Faculty of Mathematics and Natural Sciences,
Universitas Bengkulu, Bengkulu, Indonesia

Abstract

Fear and anxiety due to severe labor pains could also lead to prolonged labor. The efforts made to accelerate the second stage labor process are by providing emotional support with the support of a labor camera. The mother is allowed to observe the development state of her baby's head through video on a tablet or laptop screen. Furthermore, the mother's emotional level becomes more provoked and motivated to strain the labor process faster. This study aims to determine the effect of the labor cameras on the second state duration in primiparous. The design of this study was a posttest-only control group design experiment with a total sample of 30 primiparous of the second stage at independent midwife practice in Bengkulu city in November–December 2020. Each group consisted of 15 for treatment (with labor cameras) and 15 for control (without labor cameras)—the assessment of the labor duration by counting the labor time in seconds during the second state. The statistical results using the t test and chi-square test analysis showed that the intervention group's labor duration (1,393.3 seconds) was shorter than the control group's (2,340.6 seconds). The mean difference in the delivery time was 947.3 seconds or 15.7 minutes faster in the intervention group than in the control group. In conclusion, using a labor camera on the labor duration of the second stage in primiparous mothers is an effect of using a labor camera.

Keywords: Labor camera, labor duration, primipara

Pengaruh Kamera Persalinan terhadap Durasi Persalinan Kala II pada Primipara

Abstrak

Rasa takut dan cemas akibat nyeri persalinan yang berat juga dapat menyebabkan partus lama. Salah satu upaya yang dilakukan untuk mempercepat proses kala II persalinan adalah memberikan dukungan emosional dengan bantuan kamera persalinan. Ibu diberi kesempatan untuk melihat perkembangan pengeluaran kepala bayinya melalui video pada layar tablet atau laptop sehingga tingkat emosional ibu menjadi lebih terbangun dan termotivasi untuk mempercepat proses persalinan. Penelitian ini bertujuan mengetahui pengaruh kamera persalinan terhadap durasi persalinan kala II pada primipara. Desain penelitian adalah eksperimen *posttest-only control group design* dengan jumlah sampel 30 primipara kala II di bidan praktik mandiri Kota Bengkulu pada November–Desember 2020. Tiap-tiap kelompok berjumlah 15 untuk kelompok perlakuan (menggunakan kamera persalinan) dan 15 untuk kontrol (tidak menggunakan kamera persalinan). Penilaian durasi persalinan dengan menghitung detik selama kala II berlangsung. Pengujian statistik menggunakan analisis uji t dan uji *chi-square* menunjukkan bahwa durasi persalinan kelompok perlakuan (1.393,3 detik) lebih singkat daripada kelompok kontrol (2.340,6 detik). Selisih perbedaan waktu persalinan rerata selama 947,3 detik atau 15,7 menit lebih cepat pada kelompok intervensi dibanding dengan kelompok kontrol. Simpulan, terdapat pengaruh penggunaan kamera persalinan terhadap durasi persalinan kala II pada ibu primipara.

Kata kunci: Kamera persalinan, lama persalinan, primipara

Introduction

Labor is a natural process; the World Health Organization estimates that around 70–80% of pregnant women have a low risk from labor to birth. The progress of labor is influenced by the 5 P's, namely passage, passenger (fetus or baby), power (strength of uterus contraction), psyche (psychological condition), and position if any of the components change, the outcome of labor can be adversely affected. Prolonged labor or dystocia could increase maternal and neonatal mortality and morbidity. The failure of the labor progress is caused by mechanical problems with the mismatch between the size of the presenting part of the fetus and the mother's pelvis, malpresentation, labor in the posterior occipital position, and ineffective uterus contraction.[1–4]

Fear and anxiety due to severe labor pains could also lead to prolonged labor because stimulation of the sympathetic nervous system trigger increased catecholamine secretion. Further, it leads to increase levels of the hormone epinephrine, which results in weak uterus contraction in case uterus contraction does not align with the cervical opening.[1,5] The mothers who experience anxiety during childbirth, 30% encounter fear during childbirth. The traumatic experience of childbirth causes a more extended time interval at subsequent deliveries and increases the risk for cesarean section.[6,7] The results of a case-control study by Sydsjo et al.[6] in Southeast Sweden in 2001–2007 on 23,000 samples showed the mothers who experienced fear during childbirth were 5.2 times at risk for cesarean section, and severe fear increased labor duration by 40 minutes in the active phase (p<0.001).

The efforts are made to accelerate the second stage labor process by providing emotional support. The action given is with the support of a childbirth mirror where the mother can see the development of her baby's expenditure. Furthermore, the emotional level of the mother's emotional level becomes more provoked and motivated to strain and the labor process faster. However, the labor mirrors have limited visibility and are unsupported to see closely related to the delivery process and inflexibility in placement due to the large size of the mirror.[8–10]

The labor mirror was developed into a video directly seen and had the advantage of a wider, clearer, and closer saw range through the monitor screen. In addition, there is a zoom-in feature and more flexibility in placing cameras and monitors when considering the dimension factor and the purposes of analysis of labor in the event of a pathological condition. Furthermore, the mothers who intend to the moment documentation can be recorded using live video by using the labor camera during the labor process. The physiological effect is when the baby's head begins to provide encouragement and motivation. The video is a method to reduce pain in an active way and decrease the second stage of labor.[9,11–14]

The preliminary results of this study conducted at the independent midwife practice of Bengkulu city have not implemented a labor camera yet to assist the acceleration of the second stage of labor. For this reason, midwives must use a labor camera that can record the birth process directly and be seen through a monitor/screen on a television or other software to provide motivation and accelerate the second stage of the labor process. Therefore, this study was conducted to determine the effect of using a labor camera on the duration of second-stage labor in primiparous mothers.

Methods

The study design used an experiment with a posttest-only control group design and the sample selection using an accidental sampling technique. The study group consisted of the treatment group (with labor camera) and the control group (without labor camera) and was randomized with random permuted blocks. Labor camera was a tool designed to assist childbirth using a portable camera and motion sensor with a microcontroller. Furthermore, it was displayed on the monitor to assist the mother in seeing the delivery process.

The study was evaluated two variables; the independent variable was the labor camera used to monitor the delivery process, the dependent variable was the length of the second stage of labor, the time used from complete dilatation to the baby was born.

The research has been implemented at ten independent midwife practices in Bengkulu city from November to December 2020 and was carried out sequentially with other research teams researching appropriate technology for labor cameras. During the study period, 30 second-stage primiparous, each group amounting to 15

for treatment (with labor camera) and control (without labor camera/conventional). The subject criteria were second stage primiparous labor, single pregnancy, age 20–35 years, primipara opening 10 cm (complete), head presentation of posterior fontanel in front, 37–42 weeks of gestation, intact amniotic fluid. In addition, they also have to have good uterus contraction, regular rhythm, frequency 3× deep 10 minutes, did not get labor induction, and interpreted fetal weight >2,500 g to <4,000 g. Next, exclusion criteria: head and pelvis disproportion; hemoglobin <11 g/dL; mothers with body mass index <18.5 or ≥30; pregnancies with complications such as pre-eclampsia, eclampsia, antepartum bleeding, and contraindications for vaginal delivery; and without companions during the labor. Finally, the drop-out criteria are mothers who could not continue vaginal labor, precipitated labor, prolonged labor, assessment of the labor duration using a stopwatch with a count of seconds.

The assessment of labor duration was performed by using a digital stopwatch with a count of seconds. Further, the analysis was by bivariate analysis test. First, the characteristic data were compared using the chi-square test. Second, the data normality test was evaluated using the Shapiro-Wilk test. Finally, analysis of the time differences in labor duration in the control and treatment groups was analyzed using the t test.

The Health Research Ethics Committee of the Faculty of Medicine and Health Sciences of the Universitas Bengkulu has approved this research, with the ethics committee approval number: 324/UN30.14.9/LT/2020.

Results

The research subject is 30 respondents and divided into two groups. Each group is 30 respondents, group A, namely the treatment group with the labor camera and group B without the labor camera (conventional).

Table 1 shows that the subject's characteristics are followed by the inclusion and exclusion criteria for the study determined. The sample was 30, divided into 15 respondents in the intervention group and 15 in the control group. All respondents are recorded on education level, time of rupture of membranes, and weight of newborns.

The results of the data normality test with Shapiro-Wilk data were not normally distributed with a significance value of $p>0.05$, generally distributed in the two groups, namely, intervention and control. Thus, the purposes of the analysis used parametric statistics, namely the independent t test.

Table 2 shows that the control group's average labor duration is 1,393.3 seconds shorter than the control group's 2,340.6 seconds. The time difference in the labor duration time is 947.3 seconds or 15.7 minutes faster in the intervention group than in the control group. Based on the results of statistical testing using an unpaired t test, the probability value obtained is smaller than the predetermined significance level (<0.05). The

Table 1 Characteristics of the Research Subjects

| Characteristics | Category | | p Value* |
	Treatment (n=15)	Control (n=15)	
Education level			0.642
Low	2	1	
Middle	10	9	
High	3	5	
Time of rupture of membranes			0.000
Opening 7–8 cm	6	6	
Opening 9–10 cm	9	9	
Weight of newborn (gram)			0.593
2,500–2,900	3	3	
3,000–3,500	12	11	
3,600–4,000	0	1	

Note: *chi-square test

Table 2 Comparison of the Labor Duration in the Two Categories

Second Stage of Labor	Category		Time Difference	p Value*
	Intervention (n=15)	Control (n=15)		
Mean	1,393.3	2,340.6	947.3 seconds or	0.000
SD	263.7	334.53	15.7 minutes	

Note: *t test

results indicate a significant effect of the labor duration in the treatment group is shorter than the control group.

Discussion

The characteristics of the two groups observed are education, time of rupture of membranes, and the bodyweight of the newborn. The first characteristic is education. Most of the respondents' education is in middle-level education, both in the intervention and control groups. A person's level of education is very significant in health conditions and affects more to a person's perception of receiving better information. The participant with a high-level education will easily accept the information provided. Information about childbirth can improve the experience of mothers during childbirth so that mothers will concentrate more, and their motoric activities are focused on being able to control pain due to uterus contractions, fear, and anxiety to deal with childbirth. Labor pain, fear, and anxiety affect psychological responses that impact the progress of labor.[1,15-17]

The second characteristic of the study subjects is the time of the rupture of membranes. The characteristics of the amniotic fluid in the treatment group and the control group are mostly in the spontaneous rupture of membranes and the time of the rupture of the membranes at 7–8 cm opening. The amniotic membrane is composed of an amniotic membrane. The chorion covers the fetal surface of the placenta and forms a sac that contains the fetus and supports the fetus and amniotic fluid. The amniotic membrane produces amniotic fluid. The membranes should rupture spontaneously at the onset of labor or remain intact throughout the active labor process until the doctor or midwife decides to break the membranes or until the baby is born. Rupture of the membranes can cause the fetal head to pass through the pelvis and shorten labor duration.

When the membranes rupture, the production and release of prostaglandins and oxytocin increase so that contractions become stronger and cervical opening is faster. Pressure from the intact membrane contributes to the ripening, thinning, and opening of the cervix.[1-3,18]

The characteristics of the birth weight of the babies in both groups are in the range of 3,000–3,499 g. Baby weight is related to head circumference and shoulder width. Birth weight affects the labor duration about the size of the pelvis, which is considered sufficient to deliver a vaginal size to a normal-sized baby. The labor duration and the need for cesarean section are related to fetal weight. The number of cesarean sections doubles from 4% in infants weighing 3,500–3,999 g to 8% when the fetal weight is 4,000–4,999 g.[1-4]

Research on the second stage duration of labor shows a significant difference between the treatment group and the control group. The results supported the analysis, which could be seen from the stage of labor at the second stage. Statistical analysis also shows a significant difference between the treatment group and the control group.

The study's statistical results on the time difference in the labor duration on the second stage with and without the labor camera group show a significant difference in the two groups. In labor with the camera group, the statistical results using an independent t test show a time difference in the second stage of labor between the group with and without labor camera (p<0.05) as shown 1,393.3 and 2,340.6 seconds. The time difference in the mean duration of delivery time is 947.3 seconds or 15.7 minutes faster in the intervention group than in the control group. This situation indicates that implementing a labor camera motivates mothers to deliver when straining and accelerate the second stage of the labor in primiparous.

The results have shown a corresponding with

Doyle et al.,[9] which has been done between 2013 to 2014 in intra-natal care service centers in the USA. Five hundred respondents were researched with postpartum mothers aged 18–49 years. The results have described the frequency of using mirrors in childbirth to increase the focus on accepting and accelerating the process of expelling the baby of 53%, and 58% stated they use mirrors during the process of expelling the baby was a positive experience for them.

Becerra-Maya et al.'s[18] research results with a descriptive cross-sectional research method are conducted at the Universitario Fundación Alcorcón Hospital (Madrid, Spain). The data are collected using a 14 item scale based on a semantic differential technique developed from a pilot study with 92 subjects. The results of the study indicate 73% (95% CI=62.7 and 84.4) of the use of mirrors during the labor process support efforts to give birth and facilitate labor effectiveness. Mirrors are used to guide labor, observe the process of their baby's birth, and enhance the labor experience.

Palompon et al.'s[19] research in the Philippines examined the effectiveness of mirrors in accelerating the second stage of childbirth in primiparous with a post-test design research method with 20 primiparous respondents. The results showed that the intervention group obtained an average of 6.77 with a mean difference of 12.15 (SD=5.24). It shows a significant difference in accelerating the duration of second-stage labor.

The results of Novianti and Rokhamah's[20] research at Paru Batu Hospital, Indonesia, have shown a comparison between the two treatment and control groups in primiparous. The results showed that the mirror is an effective method because it can accelerate the second stage of labor in primigravida mothers with an average time of 13 minutes. For those who do not use a mirror, the average time required is 25 minutes.

Fear and anxiety due to severe labor pains caused prolonged labor because stimulation of the sympathetic nervous system stimulates increased catecholamine secretion, leading to increased levels of the hormone epinephrine. The results in weak uterus contraction indicate the contraction is not in line with the cervical opening.[1,2,20] The mother who has labor anxiety will increase the experience of fear by 30% during childbirth. The traumatic experience of childbirth causes a more extended time interval at subsequent deliveries

and increases the risk for cesarean section. The results of a case-control study by Sydsjo et al.[6] in Southeast Sweden in 2001–2007 with 23,000 samples showed the mothers who experienced fear during childbirth were 5.2 times at risk for cesarean section, and severe fear increased labor duration by 40 minutes in the active phase (p<0.001).

The labor mirror was developed into a video directly seen and had the advantage of a broader, clearer, and closer range through the monitor screen. In addition, there is a zoom-in feature and more flexibility in placing cameras and monitors when considering the dimension factor and the purposes of analysis of labor in the event of a pathological condition.[22,23] Furthermore, the mothers who intend to the moment documentation can be recorded using live video by using the labor camera during the labor process. The physiological effect is when the baby's head begins to provide encouragement and motivation. The video is a method to reduce pain in an active way and decrease the second stage of labor.

Many factors influence the future works, the duration of delivery. Therefore, it is necessary to do further research examining other variables that could affect the duration of labor, such as the variable anxiety factor.

Conclusion

This study concluded that using a labor camera on the labor duration of the second stage in primiparous mothers is an effect of using a labor camera.

Conflict of Interest

All authors stated that there was no conflict of interest in this article.

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RESEARCH ARTICLE

Factors Associated to Growth Disorder in Children with Thalassemia Major

Nurbaiti Annisaa Soegiharto,[1] Meiyanti[2]

[1]Medical Undergraduate Study Program, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia,
[2]Department of Pharmacology and Medical Pharmacy, Faculty of Medicine,
Universitas Trisakti, Jakarta, Indonesia

Abstract

Growth disorders in short stature are often found in patients with β-thalassemia major. It is caused by several factors such as hypoxia, hemosiderosis, deficiency of nutritional intake, and micronutrient. Disorder in growth will affect the patient's quality of life. This study aims to determine the prevalence of growth disorders and analyze the factors associated with thalassemia child growth disorders. This study used an observational analytic study with a cross-sectional design on 167 patients with β-thalassemia major at the Palang Merah Indonesia Hospital, Bogor, West Java, in October–December 2018. Data was collected using a transfusion compliance questionnaire and the Morisky Medication Adherence Scale (MMAS-8), while growth was assessed using the CDC 2000 height/age curve. Data analysis used SPSS for Windows version 21.0. Of 167 subjects, 86 subjects (51.5%) were not adherent to transfusion, 97 subjects (58.1%) had low consumption of chelation iron, and 146 subjects (87.4%) had growth problems. The results of bivariate data analysis using the chi-square test for transfusion compliance and parental education on growth obtained p=0.000 and p=0.032. Likewise, for compliance with iron chelation consumption and parents' income to growth, the p value=0.000 was obtained. It was concluded that the prevalence of growth disorders was 87.4%, and there was a relationship between transfusion compliance, parental education level, parents' income, and compliance with iron chelation consumption on growth disorders in thalassemia children.

Keywords: Growth, iron chelation, thalassemia major, transfusion

Faktor-faktor yang Berhubungan dengan Gangguan Pertumbuhan pada Anak Talasemia Mayor

Abstrak

Gangguan pertumbuhan berupa perawakan pendek sering ditemukan pada penderita talasemia β mayor. Hal ini disebabkan oleh beberapa faktor seperti hipoksia, hemosiderosis, kekurangan asupan nutrisi, dan mikonutrien. Gangguan pertumbuhan akan memengaruhi kualitas hidup pasien. Penelitian ini bertujuan mengetahui prevalensi gangguan tumbuh kembang dan menganalisis faktor-faktor yang berhubungan dengan gangguan tumbuh kembang anak talasemia. Penelitian ini menggunakan jenis penelitian observasional analitik dengan desain *cross-sectional* pada 167 pasien talasemia β mayor di RS Palang Merah Indonesia, Bogor, Jawa Barat pada bulan Oktober–Desember 2018. Pengumpulan data dilakukan dengan menggunakan kuesioner kepatuhan transfusi dan *Morisky Medication Adherence Scale* (MMAS-8), sedangkan pertumbuhan dinilai menggunakan kurva tinggi/usia CDC 2000. Analisis data menggunakan SPSS *for Windows* versi 21.0. Dari 167 subjek, 86 subjek (51,5%) tidak patuh pada transfusi, 97 subjek (58,1%) memiliki konsumsi kelasi besi rendah, dan 146 subjek (87,4%) mengalami gangguan pertumbuhan. Hasil analisis data bivariat menggunakan uji *chi-square* untuk kepatuhan transfusi dan pendidikan orangtua tentang pertumbuhan diperoleh p=0,000 dan p=0,032. Begitu pula untuk kepatuhan konsumsi kelasi besi dan pendapatan orangtua terhadap pertumbuhan diperoleh p=0,000. Disimpulkan bahwa prevalensi gangguan tumbuh kembang sebesar 87,4% dan terdapat hubungan kepatuhan transfusi, tingkat pendidikan orangtua, pendapatan orangtua, dan kepatuhan konsumsi kelasi besi dengan gangguan tumbuh kembang anak talasemia.

Kata kunci: Kelasi besi, pertumbuhan, talasemia mayor, transfusi

Correspondence: Meiyanti, dr., Sp.F.K. Department of Pharmacology and Medical Pharmacy, Faculty of Medicine, Universitas Trisakti. Jln. Kyai Tapa No. 260, West Jakarta 11440, Special Capital Region of Jakarta, Indonesia. E-mail: meiyanti@trisakti.ac.id

Introduction

Thalassemia is a blood disorder found in many countries around the world, especially in people that come from the Mediterranean, Middle East, and Asia. Thalassemia is a genetically recessive inherited blood disorder characterized by lack or absence of hemoglobin chain synthesis.[1,2] This causes the shape of blood cells to become imperfect and leads to anemia. The World Health Organization (WHO) in 2012 reported that approximately 7% of the world's population has the thalassemia gene, with 40% of cases in Asia.[3] The Indonesian Thalassemia Foundation noted an increase in cases of thalassemia major in Indonesia from year to year. In 2018 there were reported 9,028 cases. The prevalence of thalassemia carrier cases in Indonesia was estimated at 3.7%.[4] Stunted growth often occurs in pediatric β-thalassemia patients. Adolescents are generally not immediately detected in most patients.

Before the era of transfusion and iron chelation therapy, tissue hypoxia due to anemia and iron toxicity due to repeated blood transfusions were the leading causes of growth disorders. Nutrition is another critical factor for growth.[1,5] A study conducted in India found that 54% of thalassemia major children had growth problems.[6] Previous researchers concluded that various factors influenced the relationship between transfusion compliance and iron chelation consumption on growth in children with thalassemia.[7,8] Meanwhile, according to the Gomber and Dewan[9] study, it was concluded that there was no relationship between blood transfusion compliance and iron chelation consumption on growth in children with thalassemia. Another study concluded that the risk factors for growth disorders in thalassemia were age, deferoxamine dose, and family income, serum ferritin levels.[10,11] This study aims to determine the prevalence of growth disorder and to analyze the risk factors associated with growth in β-thalassemia major children.

Methods

This research was an observational analytic study with a cross-sectional design at Palang Merah Indonesia Hospital, Bogor, West Java, Indonesia, in October–December 2018. The selection of research subjects used consecutive non-random sampling techniques. Data were collected by interview using two questionnaires, namely a transfusion compliance questionnaire recommended by the Minister of Health of the Republic of Indonesia. It consists of 4 questions and a questionnaire on compliance with iron chelation drinking using Morisky Medication Adherence Scales (MMAS-8) consisting of 8 question items. Each item is given a one if the answer is true and 0 if the answer is wrong. The level of adherence was divided into three categories: high adherence if the score was 8, the score 6–7 was moderate, and the score <6 was low. Growth impairment assessments used the 2000 stature for age percentile CDC curve. If the result is <5 percentile, it is said to have growth problems. Measurement of body height using a microtoise with a measuring capacity of 2 meters and an accuracy of 0.1 cm.

The study inclusion criteria were β-major thalassemia patients aged 7–16 years who received blood transfusions and iron chelation therapy, parents/guardians of patients willing to sign an informed consent. The sample size was determined using the infinite-finite population formula with a 95% significance level of 1.96. The prevalence for counting samples was 54.4%, with a measurement accuracy of 0.05. Based on the calculation, it is required that the research subjects are 167 thalassemia major patients aged 7–16 years. The data processing used SPSS for Windows version 21.0, and data analysis used the chi-square test with a significance level of ≤0.05. This research protocol has passed a research ethics review from the Research Ethics Committee of the Faculty of Medicine, Universitas Trisakti number: 137/KER-FK/VIII/2018.

Results

The results obtained from 167 research subjects were most girls as many as 95 subjects (56.9%). Most of the subjects were ≤15 years old (70.7%), with an average age of 12 years, 132 cm height, and 34 kg body weight. A total of 86 subjects (51.5%) were included in the non-adherent category for blood transfusion, 97 subjects (58.1%) were in the low category for adherence to iron chelation consumption. The prevalence of growth disorders was found 87.4% of subjects, 70.1% with Hb levels ≤7 g/dL and 70.1% had ferritin levels ≥1,000–<2,500 ng/mL. From the parental data, it was found that most parents had a moderate

Table 1 Characteristic of Research Subjects

Variables	x±SD	n=167	%
Gender			
Boy		72	43.1
Girl		95	56.9
Age (year)	12±3.90		
Height (cm)	132±18.50		
Body weight (kg)	34± 12.10		
Parent education			
Low		28	16.8
Middle		82	49.1
High		57	34.1
Parent income			
<regional minimum wage		88	52.7
≥regional minimum wage		79	47.3
Siblings (+thalassemia major)			
Yes		15	9.0
No		152	91.0
Transfusion compliance			
Yes		81	48.5
No		86	51.5
Compliance iron chelation			
Low		97	58.1
Middle		48	28.7
High		22	13.2
Growth disturbance			
Yes		146	87.4
No		21	12.6
Pre-transfusion Hb (g/dL)			
≤7		117	70.1
>7		50	29.9
Ferritin level (ng/mL)			
<1,000		7	4.2
≥1,000−<2,500		117	70.1
≥2,500		43	25.7

level of education (graduated from high school) is 49.1%, and parents' income is below the regional minimum wage of 52.7%. In the family other than the subject, it was found that 9% (15 of 167 subjects) had siblings with thalassemia as well (Table 1).

This study found a statistically significant relationship between transfusion adherence factors, parental education, and growth disorders with p=0.000 and p=0.032. Similarly, there was a statistically significant relationship between parents' income factors and compliance with iron chelation consumption with growth disorders with p=0.000 and p=0.000 (Table 2).

Discussion

This study found that 87.4% of the 167 subjects with β-thalassemia major had growth problems. The prevalence obtained is higher than previous studies conducted in India; 54% of thalassemia major children have growth problems.[6] Growth disorders in the form of short stature, with a height below the average, are often found in patients who do not routinely perform blood transfusions or consume chelating iron regularly according to doctor's instructions. Many factors cause growth disorders such as chronic anemia and hypoxia with the clinical picture of children

Table 2 Bivariate Relationship between Independent Variables and Growth Disorder

Variables	Growth Disorder (n=167)		p Value
	Yes (%)	No (%)	
Transfusion compliance			0.000[*]
Yes	60 (74.1)	21 (25.9)	
No	86 (100)	0 (0)	
Parent education			0.032[*]
Low	27 (96.4)	1 (3.6)	
Middle	77 (93.9)	5 (6.1)	
High	42(73.7)	15 (26.3)	
Parent income			0.000[*]
<regional minimum wage	88 (100)	0 (0)	
≥regional minimum wage	58 (73.4)	21 (26.6)	
Compliance iron chelation			
Low	97 (100)	0 (0)	0.000[*]
Moderate	45 (93.8)	3 (6.3)	
High	4 (18.2)	18 (81.8)	

Note: [*]p<0.05 significant

who are pale, weak, and easily tired as well as due to liver dysfunction, deficiency of zinc and folic acid, iron overload, iron chelation toxicity, emotional factors, and endocrine disorders.[12–14]

Adherence to blood transfusion on research subjects showed low-level adherence. Factors that influence this condition were psychosocial factors, economic conditions, worry/fear of other risks from blood transfusions such as hepatitis infection and HIV.[13,15] Physical changes in thalassemia children make parents feel embarrassed and cover the child's condition from the community. Economic problems also play a role in the level of transfusion compliance. Even though they have used government health insurance coverage and are not charged for blood transfusions, patients still have to pay for transportation, which prevents patients from going to the hospital for blood transfusions. If blood transfusions are given regularly, and Hb levels are maintained at ≥9 g/dL, children with thalassemia will experience average growth and development until 10–12 years.[5,16]

Repeated blood transfusions will lead to the fulfillment of transferrin capacity in the body, which will cause iron overload. Iron accumulation occurs in various organs such as the liver, pancreas, heart, endocrine glands, and gonads. Free iron/non-transferrin binding protein (NTBI) acts as a free radical and can cause damage to cells and organ tissues. Iron

accumulation in the endocrine glands causes endocrine disorders causing hypogonadotropic, adrenal insufficiency, growth hormone (GH) deficiency, hypothyroidism, hypoparathyroidism, hypogonadism, and diabetes mellitus.[16–19] Growth disturbances in thalassemia major patients due to hormonal disorders are very complex. This growth disturbance occurs due to iron overload in the endocrine and gonadal glands, which causes hypogonadotropic hypogonadism, hypothyroidism, hypoparatiorids, diabetes mellitus, growth hormone deficiency, adrenal insufficiency.[20–22] Iron overload in the anterior pituitary gland causes pituitary damage, resulting in disruption of GH pathways-IGF-I (growth hormone-insulin-like growth hormone factor-I). Damage to the anterior pituitary causes impaired GH secretion, which results in impaired production of IGF-I and IGFBP3 by the liver due to reduced GH stimulation of the liver, resulting in decreased GH and IGF-I. It will affect the speed of bone growth on the bone growth plate so that the child's stature is short.[17,18,23]

Hypogonadotropic-hypogonadism happens due to damage to the hypothalamus and anterior pituitary caused by hemosiderosis. The gonadotropins produced by the anterior pituitary are very sensitive to oxidative damage caused by iron overload. Several studies have reported hypothyroidism in β-thalassemia major. As is known, thyroid hormone plays an essential role

in bone maturation, influencing GH secretion, directly affecting chondrocytes by increasing IGF-I secretion, and promoting chondrocyte maturation. The hypothyroid condition will play a role in the growth disorders of thalassemia major children.[19,20] Iron chelation is needed to overcome iron overload and hemosiderosis. Iron chelation therapy requires high commitment and compliance from the patient and family support and community support among thalassemia. The choice of iron chelation for each individual can be different by considering several things: effectiveness, side effects, drug availability, price, patient's quality of life, patient comfort because it must be used continuously. Currently, in Indonesia, there are three types of chelation iron, namely deferoxamine, deferiprone, and deferasirox. Although the administration of iron chelation is provided free of charge by the government, it appears that patient adherence to iron chelation consumption is low. Many things can affect compliance with iron chelation consumption. The low level of adherence to iron chelation consumption is influenced by patient psychological factors (the patient feels bored), side effects of the drug, and also the availability of drugs.

Low adherence to the use of iron chelation was statistically significant to growth disorders. Previous researchers also concluded that irregular consumption of chelation iron would affect the growth of thalassemic children.[7] In contrast to the results obtained in this study, other researchers concluded that there was no relationship between transfusion adherence and consumption of chelating iron on growth.

In this study, there is a significant relationship between education level and family income with growth disorders. It also correlates with parents' understanding of the disease, management in routine transfusions, the benefits of iron chelation, and the prevention of having the next child with thalassemia major. In addition, nutritional factors are also important things to pay attention to in this case. Multifactor cause growth disturbances in thalassemia patients. Factors that more influence growth and can cause growth disorders are ethnic, genetic, and hormonal factors. Nutritional deficiencies, deficiency of vitamin C, vitamin D, lack of physical activity and psychological disorders also contribute to growth disorders in thalassemia major patients.[9–11] Cooperation, communication

and good relations between parents and other parents of fellow patients, parents and health workers, both doctors, nurses and pharmacists are needed to overcome problems that arise from this disease.[24,25] Further research is needed to research other factors that can affect growth disorders in children with thalassemia, such as psychological, nutritional, ethnic, genetic, and hormonal factors.

Conclusions

This study concluded that there was a significant relationship between transfusion compliance with iron chelation consumption and the level of parental education and parents' income on growth in children with β-thalassemia major.

Conflict of Interest

The authors do not have any conflict of interest to declare.

Acknowledgments

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RESEARCH ARTICLE

Stakeholder Perception towards the Implementation of National Health Insurance Program

Yuli Susanti,¹ Tita Barriah Siddiq,² Siska Nia Irasanti,¹ Rizki Perdana,³ Yusuf Heriady⁴

¹Department of Public Health, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
²Department of Medical Education, Bioethics, Humanities and Islamic Insert, Faculty of Medicine,
Universitas Islam Bandung, Bandung, Indonesia, ³Department of Anatomy, Faculty of Medicine,
Universitas Islam Bandung, Bandung, Indonesia, ⁴Department of Surgery, Faculty of Medicine,
Universitas Islam Bandung, Bandung, Indonesia

Abstract

Indonesian National Health Insurance (NHI) is a social protection program that ensures the fulfillment of basic needs for proper health by implementing a quality and cost control system. There are still differences in perceptions and complaints felt by patients regarding the implementation of the NHI program. The purpose of this study was to evaluate the implementation of the NHI program based on the perception of all stakeholders in the aspect of health equity, quality of service, and health financing. Quantitative research methods with survey techniques on 204 respondents were selected by stratified random sampling in Al-Ihsan Regional General Hospital West Java Province from January to May 2021. The data were analyzed by using the Kruskal-Wallis test and Mann-Whitney U test on the perception of the stakeholder groups. The results showed that the aspects of health equity, service quality, and health financing on the implementation of the NHI program were in a good category. The increase in Healthcare and Social Security Agency (HSSA) insurance premium was considered the lowest aspect. There were significant differences in the perception of stakeholder groups on the aspects of health equity, service quality, and health financing. There were significant differences in perceptions of health equity based on the ages groups and in perceptions of health financing based on income. This indicates that stakeholders' perceptions of the NHI program affected some conditions, including roles in services, ages, and income.

Keywords: National health insurance, perception, stakeholder

Persepsi *Stakeholder* terhadap Implementasi Program Jaminan Kesehatan Nasional

Abstrak

Jaminan Kesehatan Nasional (JKN) merupakan program perlindungan sosial yang menjamin pemenuhan kebutuhan dasar kesehatan yang layak melalui penerapan sistem kendali mutu dan biaya. Masih terdapat perbedaan persepsi dan keluhan yang dirasakan pasien terhadap pelaksanaan program JKN. Tujuan penelitian ini mengevaluasi pelaksanaan program JKN berdasar atas persepsi seluruh *stakeholder* pada aspek *health equity* (pemerataan), mutu layanan, dan pembiayaan kesehatan. Metode penelitian kuantitatif dengan teknik survei pada 204 responden yang dipilih secara *stratified random sampling* di RSUD Al-Ihsan Provinsi Jawa Barat periode Januari–Mei 2021. Analisis data menggunakan Uji Kruskal-Wallis dan Mann-Whitney U terhadap persepsi kelompok *stakeholder*. Hasil penelitian menunjukkan bahwa aspek *health equity*, mutu layanan, dan pembiayaan kesehatan pada implementasi program JKN berada dalam kategori baik. Kenaikan premi asuransi BPJS Kesehatan dinilai paling rendah. Terdapat perbedaan signifikan persepsi antara kelompok *stakeholder* pada aspek *health equity*, mutu layanan, dan pembiayaan kesehatan. Terdapat perbedaan signifikan persepsi terhadap *health equity* berdasar atas kelompok usia dan persepsi pada aspek pembiayaan kesehatan berdasar atas pendapatan. Hal ini menunjukkan bahwa persepsi *stakeholder* terhadap program JKN dipengaruhi beberapa kondisi, antara lain peran dalam layanan, usia, dan pendapatan.

Kata kunci: Jaminan kesehatan nasional, persepsi, *stakeholder*

Introduction

Universal health coverage (UHC) implies that all people have access to quality health services without worrying or experiencing difficulties paying for health care. Health equity can only be achieved if each individual has the opportunity to maintain his/her health potential.[1] The National Social Security System or *Sistem Jaminan Sosial Nasional* (SJSN) is a program of the Indonesian Government to assure social protection and welfare for all people.[2]

Jaminan Kesehatan Nasional (JKN) or the National Health Insurance (NHI) program is part of the SJSN to provide insurance in the health sector. The implementation of the NHI program using the principles of managed care is a technique that uses an integrated approach and the financing of health services through quality control and cost control by increasing the feasibility and efficiency of health services.[3,4]

One of the main objectives of the NHI program is to improve equity in access to health services. Several previous studies prove that health insurance has a positive impact on improving access to health care.[5–7] The NHI program has an impact of 2.4% on access to inpatient care at the hospital.[6] The broader the participation of NHI so participants can more widely use the benefits package guaranteed by NHI. Optimization of healthcare utilization by participants must be supported by the equitable distribution of health facilities and personnel.[8]

The implementation of a quality control system for health insurance services must be carried out comprehensively, including meeting the quality standards of health facilities, ensuring that the health service process runs according to established standards, and monitoring participants' health outcomes.[9]

The high number of referrals to advanced health services (hospitals) increases health costs, which burden the Government's budget. Furthermore, they are not following the quality control and cost control principles implemented by *Badan Penyelenggara Jaminan Sosial Kesehatan* (*BPJS Kesehatan*) or the Healthcare and Social Security Agency (HSSA). The HSSA underwent a deficit in health financing during six years of program implementation because of the premium below an actuary cost.[10] The inequalities of HSSA's tariff than the actual cost issued of health services indicate that

the NHI program's implementation in the funding aspect is not run optimally.[11,12] At the primary level of service, the doctor's perception about the NHI program has been informed. However, there is still a complaint about the socialization of the program and capitation late payment.[13]

Perception is a process related to the entry of messages or information into the human brain, through human perception continuously in contact with the environment. This connection is carried out through sight, listener, touch, taste, and smell.[13] Problems that arise in health services can be caused by a lack of information and differences in perceptions among stakeholders in implementing the NHI program.

There are different perceptions between the premium receiver and the non-receiver based on the provision of information implementation and pay the benefits or HSSA health services finance in Sleman.[14] Another problem arises from health workers both at the hospital and primary health facilities. There are 47.6% of specialist doctors felt that they were not satisfied with the NHI program, and there is the relationship between satisfaction with Indonesian Case-Based Groups (INA-CBGs) knowledge, the work environment, remuneration, transparency, and hospital policy at dr. Zainoel Abidin Regional General Hospital.[15]

Health service management consists of at least three groups of people involved. First is the human health service provider (health providers, for example, doctors, nurses), Second, the health service recipient group (consumers), and the third group, who are indirectly involved, are the administrator (both among companies and governments and others).[16]

The purpose of this study was to analyze the difference of perception between stakeholders who play a role in the implementation of the NHI program in hospitals within three aspects; equity of health, quality of service, and health financing. The stakeholders are health providers or health workers, hospital management, employees, patients, and the team of HSSA. The results of the study can be used for the improvement of the NHI program in the future.

Methods

This study used quantitative methods with a cross-sectional design—a survey used to gather data. The questionnaire consisted of 33 questions to assess three aspects of the implementation

Table 1　Questionnaire Dimensions

Variables		Statement Items
Equity (equalization)		
Availability of health facilities	1	In your opinion, are medical facilities (such as the number of inpatient rooms, operating rooms, medical equipment, and laboratories) fully available in this hospital?
	2	Are non-medical facilities (such as parking lots, prayer rooms, canteens, waiting rooms, breastfeeding rooms, and toilets) available in full at the hospital?
	3	Does the hospital have sufficient supporting examination facilities/equipment (such as laboratories, radiology, physiotherapy, and pharmacies).
Number of health workers/human resources	4	Does the hospital have a sufficient number of doctors/specialists for health services
	5	Does the hospital have sufficient number of health personnel (nurses, pharmacists, radiographers, analysts, and nutrition officers) for services?
	6	Does the hospital have sufficient number of non-medical employees (security guard, administration officer, customer service, and cleaning service)?
Ease of access	7	Is the location of the hospital easily accessible/reachable (strategic)?
	8	In your opinion, is registration at the hospital easy to do?
	9	In your opinion, is information about the doctor's schedule and types of services at the hospital easy to obtain?
Medical service development (within the past year)	10	Did the hospital open a new polyclinic for service development in the past year
	11	Did the hospital have a new type of service for service development in the past year
	12	Did the hospital have additional supporting equipment/new medical examinations
Quality of service		
Reliability	13	Does the hospital have a reliable doctor/specialist in medical services?
	14	Does the hospital have health workers (nurses/midwives/analysts/nutritionists) who are reliable in non-medical services?
	15	Does the hospital have employees who are reliable in non-medical services (security, registration, customer service, cleaning service, billing)
Responsiveness	16	Are the medical personnel (doctors/nurses) and hospital employees quick to respond in handling patient complaints?
	17	In your opinion, has the time to wait for service in the hospital met your expectations?
	18	Are the administrative services at the hospital are implemented quickly? (payment/cashier)
Assurance	19	Are you sure about the medical services at this hospital?
	20	Are you sure about the effectiveness of the treatment given by medical personnel?
	21	Do medical and non-medical services in hospitals comply with the hospital minimum service standards for the NHI program?
Tangible	22	Does the area/place for medical services in the hospital meet your expectations?
	23	Have the non-medical facilities at the hospital (parking area, prayer room, canteen, waiting room, park) met your expectations?
	24	Has the hospital's medical equipment met your expectations?
Empathy	25	Are the doctors at the hospital able to understand the condition that the patient feels/empathize with?
	26	Are the health workers (nurses/midwives) at the hospital able to understand the patient's condition/empathy?
	27	Are the hospital employees able to understand the patient's/empathetic condition?
Health financing		
Increase in HSSA premiums & health financing deficit	28	Do you agree with the increase in HSSA contributions?
	29	Can the increase in HSSA insurance premium contributions help the health financing deficit experienced by HSSA?
Clinical pathway	30	Is the tariff for health services (according to the class in the hospital) in accordance with the benefits you get?
	31	Are Tariff adjustments/changes required for the HSSA service package?
Participant compliance	32	Do the compliance with payment of the HSSA participant contributions every month need to be implemented?
	33	Is it necessary to disseminate information about the benefits and compliance with the payment of the HSSA participant?

of the NHI program. They are equity of health, quality of service, and health fund.

The questionnaire in this study consisted of three parts. The first part was screening questions that explain the study's objectives and classify respondents' consent about participation in the study. The second part contained the respondent's identity, and the third part included a list of questions regarding the study's variables, namely equity, quality of service, and health financing. The questionnaire used in this study can be seen in Table 1.

An instrument in this study has been undergone a validity and reliability test. The validity test was determined using the correlation Pearson product-moment according to the ordinal data scale. The item is valid if the critical r value>r table value (0.361). The reliability test uses the method Cronbach alpha. A constructor variable is reliable if the coefficient reliability value is>0.60.[17]

Data collection was carried out on stakeholders involved in implementing the NHI program at Al-Ihsan Regional General Hospital West Java Province, namely groups of doctors/specialists, patients, hospital management, nurses, midwives, hospital employees, and the HSSA team, from January to May 2021. Respondents were selected using a stratified random sampling technique with a total of 204 respondents, with the distribution of stakeholder groups as shown in Table 2. The samples met the inclusion criteria: 1. HSSA participants, 2. have used HSSA services at Al-Ihsan Regional General Hospital West Java Province, 3. aged 18–67 years, and 4. can read and access google forms via smartphone. Respondent profile that met the inclusion criteria can be seen in Table 3.

The assessment used the five-point Likert response format (ranging from 5=very good to 1=very bad). First, data analysis in this study was univariate to provide an overview of the

Table 3 Characteristics of Respondents

Variables	n=204	%
Age (years)		
25	13	6.4
26−35	79	38.7
36−45	53	26.0
46−55	39	19.1
56−65	16	7.8
>65	4	2.0
Gender		
Man	70	34.3
Woman	134	65.7
Profession		
Housewife	30	14.7
Civil servants	36	17.6
Private employees	118	57.9
Entrepreneur	2	1.0
Others	15	7.4
Not yet working	3	1.5
Education		
Elementary school	7	3.4
Junior high school	11	5.4
Senior high school	28	13.7
Higher education (diploma/bachelor/ magister/doctoral)	158	77.5
Income		
<regional minimum wages	50	24.5
≥regional minimum wages	154	75.5

perceptions of each stakeholder towards the study's variables, namely health equity, quality of service, and health financing. After that, the data was followed by bivariate analysis using the Kruskal-Wallis test to evaluate differences of perception between six stakeholder groups towards implementing the NHI program and the Mann-Whitney U test to evaluate the perceptual difference in two groups of respondent profiles.

This study had been approved by the Health Research Ethics Committee of the Universitas Islam Bandung, Indonesia, by issuing the ethical clearance number: 107/KEPK-Unisba/XII/2020.

Results

Table 4 showed that stakeholders perceived or assessed the health equity in the range of the good category (3.4–4.19). The number of health workers/human resources (HR) dimension is the lowest score in the health equity variable compare

Table 2 Stakeholder Group

No.	Stakeholders	n=204	%
1	Doctor/specialist doctor	34	16.7
2	Patient	53	26.0
3	Nurse/midwife	60	29.4
4	Hospital employees	48	23.5
5	Hospital management	5	2.5
6	HSSA team	4	2.0

Table 4 Stakeholders Perception

Variables	Dimensions	Stakeholders Perception						Total Score	Results
		Doctor/ Specialist	Hospital Employees	Hospital Management	Patient	Nurse/ Midwife	HSSA Team		
Equity	Availability of health facilities	3.95	4.29	4.73	4.06	4.38	3.58	4.17	Good
	Number of health workers/HR	3.92	4.11	4.20	3.72	4.18	4.00	4.02	Good
	Ease of access	3.74	4.19	4.73	3.99	4.09	4.25	4.17	Good
	Medical service development (within the past year)	3.94	4.24	4.87	3.95	4.33	3.67	4.17	Good
Quality of service	Reliability	3.90	4.26	4.80	4.12	4.43	3.75	4.21	Very good
	Responsiveness	3.51	3.96	4.47	3.57	3.92	3.33	3.79	Good
	Assurance	4.07	4.25	4.93	4.07	4.37	4.25	4.32	Very good
	Tangible	3.66	4.13	4.33	3.75	4.10	4.00	4.00	Good
	Empathy	3.88	4.15	5.00	3.90	4.22	4.58	4.29	Very good
Health financing	Increase in HSSA premiums and health financing deficit	2.93	2.81	1.90	2.60	2.96	1.38	2.43	Poor
	Clinical pathway	3.62	3.91	3.40	3.46	3.80	3.63	3.64	Good
	Participant compliance	4.55	4.67	4.90	4.17	4.57	4.38	4.54	Very good

Note: bad=1.0–1.79; poor=1.8–2.59; fair=2.6–3.39; good=3.4–4.19; very good=4.2–5.0

to the other dimensions but still in the good category (score 4.02). Average assessment of all stakeholders perceiving service quality variables in the good category, the responsiveness are the lowest score dimension in service quality variable (score 3.79). The health financing variable was assessed in the range of good category. However, the dimension of increased HSSA premiums and health financing deficit was the lowest score (2.43) with the poor category.

Statistical test was intended to analyze differences in perceptions between the six groups of stakeholders in assessing the implementation of the NHI program (Table 5). The hospital management group showed the highest perception toward the aspect of health equity, then nurses/midwives and by employees. Meanwhile, doctors, patients, and the HSSA team have a lower average perception value than other stakeholders. The results of the Kruskal-Wallis test showed a p value of 0.000 less than 0.05, meaning that there was a significant difference in perceptions toward the implementation of the NHI in terms of health equity as seen by six stakeholders.

The average value of perceptions of service quality from the six stakeholders had different values, which the highest perception is shown

by hospital management, nurses/midwives, and employees. Meanwhile, doctors, patients, and the HSSA team had a lower average perception value than other stakeholders. The Kruskal-Wallis test showed a p value of 0.000 less than 0.05. It means there was a significant difference in the perception of the implementation of the NHI in terms of service quality as seen by six stakeholders.

The highest stakeholder perceptions toward health financing were shown by doctors, employees, and nurses/midwives. Meanwhile, patients and the HSSA team had a lower average perception score compared to other stakeholders from the hospital management. The results of the Kruskal-Wallis test showed a p value of 0.002 less than 0.05, meaning that there was a significant difference in perceptions of the implementation of the NHI in terms of health financing based on six stakeholders.

The respondent profile showed there were significant differences in perceptions of health equity based on ages (p value<0.05). There was no significant difference in perceptions of service quality based on ages, gender, education, and income (p value>0.05). There was a significant difference in perception based on income (p value<0.05). Stakeholders with income more

Table 5 Statistical Test Result

Stakeholders	Implementation of NHI		
	Health Equity	**Quality of Service**	**Health Financing**
	X±SD	**X±SD**	**X±SD**
Groups			
Doctors	46.7±6.1	57.1±8.9	22.2±3.8
Hospital employees	50.5±6.5	62.2±9.1	22.8±3.5
Hospital management	55.6±2.7	70.6±2.9	20.4±4.7
Patients	47.2±7.4	58.2±9.6	20.4±3.6
Nurses/midwives	50.9±5.9	63.2±8.1	22.7±3.1
HSSA team	46.5±7.6	59.8±17.6	18.8±0.5
p value[a]	0.000	0.000	0.002
Age (years)			
25	49.8±5.5	60.5±6.2	22.5±2.5
26−35	50.6±6.5	62.5±9.3	22.4±3.6
36−45	49.7±5.7	60.2±9.2	21.7±4.0
46−55	48.4±8.1	60.3±10.3	21.3±3.6
56−65	44.5±6.9	57.8±8.1	21.0±2.6
>65	45.4±7.1	53.6±13.9	21.6±4.9
p value[a]	0.026	0.194	0.459
Gender			
Man	48.1±7.6	59.9±10.8	21.2±3.8
Woman	49.7±6.2	61.2±8.6	22.3±3.4
p value[b]	0.149	0.696	0.057
Education			
Elementary school	47.7±11.8	62.7±12.5	21.9±4.4
Junior high school	47.6±6.4	59.3±6.3	21.4±2.5
Senior high school	47.5±8.2	58.3±10.5	20.4±3.3
Higher education	49.6±6.2	61.2±9.2	22.2±3.6
p value[a]	0.368	0.406	0.072
Income			
<regional minimum wages	48.0±7.7	58.7±11.0	20.7±3.9
≥regional minimum wages	49.6±6.4	61.4±8.8	22.3±3.4
p value[b]	0.120	0.113	0.015

Note: [a]Kruskal-Wallis test, [b]Mann-Whitney test

than minimum regional wages have better perceptions of the health financing aspect than lower wages.

Discussion

The aspect of health equity was divided into four dimensions: the availability of facilities, the number of HR both health workers and supporting personnel, ease of access, and development of medical services. The service quality aspect was divided into five dimensions: reliability, responsiveness, assurance, tangible, and empathy. Finally, the health financing aspect was divided into three dimensions: the increase in HSSA premiums and health financing deficits,

clinical pathways, and participant compliance. Based on the evaluation of stakeholders' perception shown in Table 4, aspects of health equity were in a good category. The dimension of the availability of human resources was assessed as lower than the other dimensions but still in the good category (score 4.02)—other dimensions such as the availability of facilities, accessibility, and development services to assess equalization health.

The majority of stakeholders agree that access to health services in the hospital was easy, and the hospital provides medical and non-medical facilities to support health services. The hospital is a referral hospital province with 450 beds with different classes of care. Also, it has flagship

services, namely integrated cancer services, diabetic center, cardiac center, and supporting diagnostic radiology.[18] This is consistent with several studies showing that the NHI program has been able to improve equitable access to health services which can be seen from the increasing number of NHI participants, where previously many people with low income and are vulnerable to have less access than a middle-class society with high income.[7,19]

The supply aspect plays a role in improving access to healthcare. The optimization of healthcare utilization must be supported by the equitable distribution of health facilities and personnel.[8] Provision of health facilities is the obligation of the local and central government. It emphasized in Presidential Regulation No. 82 of 2018 concerning the obligations of the central and local governments in providing health facilities and infrastructure as an effort to meet the medical needs of the NHI participants.[19,20]

The adequacy of medical personnel in order to support healthcare was optimal. However, the number of health workers/HR was lower than the other dimensions on the health equity variable but still in the good category. The hospital has 607 health workers consisting of doctors/specialists, nurses, and midwives.[18] The ratio of health workers per population in West Java Province has exceeded the World Health Organization (WHO) standard, such as 1:11 to a general practitioner and 1:77 to nurse.[21]

The health insurance benefits for the NHI participants are individual health services. They include promotive, preventive, curative, and rehabilitative services, including drug services, medical devices, and medical consumables following medical needs. It can be said that the health service benefits package guaranteed by the NHI program fulfills the basic needs of health services. The number of health facilities that cooperate with the HSSA is quite a lot.[10]

Increased access must also be followed by improving the quality of service. The availability and distribution of health facilities and human resources can affect the quality of services. This study assessed service quality based on five dimensions, reliability, responsiveness, assurance, tangible, and empathy. The assessment of stakeholder perceptions shown in Table 4 showed that the service quality aspect was in a good category.

Stakeholders assessed using the three dimensions of service quality, reliability,

assurance, and empathy showed the very good category. The responsiveness has a lower score than the other dimensions. However, they are still in the good category. The responsiveness is associated with the speed of services and waiting time for administrative and medical treatment. The perception of stakeholders in the patient groups gave a low score on the waiting time of services in a hospital. According to other studies, the increase in HSSA participants impacted the number of patient visits to hospitals, resulting in a longer waiting time for services.[22,23] The importance to create a strong relationship between patients and hospital personnel and the need for hospital staff to be responsive, credible, and empathetic when dealing with the patients.[24]

The concept of affordable health facilities can be seen from the cost side. In this case, the NHI has provided medical expenses for participants who require health services.[25] The NHI program was run by the social insurance mechanism for six years of its implementation. The HSSA, as the institution designated to deliver the NHI program, always experience a deficit. The deficit amount is increasing every year. The discussions among academic forums always state that the amount of HSSA contributions set by the government from 2014 to 2020 is underpriced as the root of the deficit problem.[10]

The process of health services cannot be separated from health financing. Health costs are the number of funds provided to organize and or utilize various health efforts required by individuals, families, groups, and communities. The mismatch of HSSA rates compared to the real costs incurred in health services indicated that the implementation of NHI in the financing aspect has not been running optimally.[10–12]

The assessment of stakeholder perceptions toward implementing the NHI program in health financing was in a good category. However, stakeholders rated the lowest on the dimensions of the increase in HSSA insurance premiums. In addition, stakeholders assessed that the benefit packages received by participants were following the payments made. All stakeholders agreed that participant compliance was required to pay HSSA insurance premiums so that the NHI program does not experience a deficit in its implementation. Most of the stakeholders in this study (75.5%) have income more than regional minimum wages, and most of them are hospital employees that have insurance from the office.

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have not established a mechanism to impose sanctions for non-compliance in paying HSSA contributions, especially for PBPU participants who register independently. As a result, many segments of PBPU participants tend to take advantage of NHI when they need it, and after that, they wait to pay their dues regularly.[10,12]

Based on the statistical test result shown in Table 5. There were still differences in perception among the six stakeholder groups for implementing the NHI program in the hospital. The hospital management groups, nurses/midwives, and hospital employees gave the highest perception toward the aspect equity of health and service quality. This is because the hospital management and employee group have more contact with administrative, governance, and managerial activity, so they have better perceptions of equity of health and service quality. Whereas the nurses/midwives group, besides having duty on patient care, also have other duties to manage administrative for inpatient and outpatient.

The highest stakeholder perceptions toward the health financing aspect were shown by doctors, employees, and nurses/midwives. This is because the group of health workers provides health services directly to the patients, and not all the health services into the benefits package that HSSA insurance covers, so they gave a better perception of the health financing aspect.[26]

Perception is a process related to the entry of messages or information into the human brain, through human perception continuously in contact with the environment.[13] Processing sensory information and relating to past experiences enables one to create a lens in which to view the world through a filter of sociocultural influences.[27] There are the factors that influence and contribute to determining the perception. This factor includes functional or personal factors and structural factors.[28]

Based on the respondent profile, there were significant differences in perceptions of health equity based on ages (p value<0.05), and the adult group (ages 25–45 years old) has better perception. The administrative process and development of information technology such as enrollment online are more comprehensible for the adult group. Personal factors that influence the perception consist of the needs, experiences, past, motivations, hopes, desires, attention, emotions, values, memory, and mood.[28]

There were no significant differences in perceptions of service quality based on ages, gender, education, and income (p value>0.05). This showed that HSSA had provided health services equally without differentiating patients based on the class of service. It follows the mandate of the law and the NHI principle to provide fair and equitable health services.[2,29]

There was a significant difference in perception based on income (p value<0.05). Stakeholders with income more than minimum regional wages have a better perception of the health financing aspect. It is in line with the theory that status, needs, and conditions influence perception. Higher-status people can exert influence on perception than low-status people.[30]

The statistical test result showed significant differences between the perception of the six stakeholder groups in assessing the implementation of the NHI program at Al-Ihsan Regional General Hospital West Java Province on health equity, service quality, and health financing. Thus, even though the health equity, service quality, and health financing aspects studied have been running well, they still have opportunities for improvement. Therefore, none of the three aspects are included in the very good/satisfying category.

Conclusions

The results showed that the stakeholder's perception towards implementation of the NHI program was in a good category in health equity, service quality, and health financing. The increase in HSSA insurance premiums as the lowest dimensions should focus on attention that must be solved without increasing HSSA insurance premiums. The differences in perceptions on groups of stakeholders towards the implementation of the NHI program could cause problems if not handled properly. It is still needed to conduct socialization and cooperation of all stakeholders to make the service and utilization of the NHI program run optimally for mutual interest.

Conflict of Interest

No conflict of interest.

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RESEARCH ARTICLE

Identification of Health Knowledge of Lung Function in Predicting Respiratory Disorders in Smokers

Amelia Lorensia,[1] Rivan Virlando Suryadinata,[2] Lalita Tirsa[1]

[1]Department of Clinical-Community Pharmacy, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia, Salatiga, Indonesia, Nursing Study Program, Faculty of Medicine and Health Sciences, Universitas Kristen Satya Wacana, Salatiga, Indonesia

Abstract

Chronic obstructive pulmonary disease (COPD) is a high risk for active smokers. Early assessment of the condition of lung function is needed to prevent a decrease in lung function. Knowledge of self-management that determines lung health. The purpose of this study was to determine the knowledge of lung function health in predicting respiratory disorders. The study design was a case-control from August 2018 to January 2019. Data was collected through a questionnaire, namely a lung health knowledge questionnaire consisting of categories: risk factors, symptoms, and therapy for respiratory disorders. The research sample was adult men who work in the transportation sector in Surabaya city using purposive sampling. Data analysis using chi-square. The data obtained were 300 people, consisting of 126 people without lung function disorders and 174 people with pulmonary function disorders. The risk factor knowledge category showed a significant difference (p=0.000) between the group, with the most disorders at the low knowledge level (42.0%). The symptom knowledge category showed a significant difference (p=0.000) between groups, and most of the groups with disorders were at a low knowledge level (55.8%). The category of knowledge of respiratory symptoms showed a significant difference (p=0.000) between groups, with the knowledge level in both of them mostly at a sufficient level. Therefore, low lung function health knowledge reflects low lung function conditions.

Keywords: Knowledge, lung function, smokers

Identifikasi Pengetahuan Kesehatan Fungsi Paru dalam Memprediksi Gangguan Pernapasan pada Perokok

Abstrak

Penyakit paru obstruktif kronik (PPOK) berisiko tinggi dialami oleh perokok aktif. Pengkajian dini terhadap kondisi fungsi paru diperlukan untuk mencegah penurunan fungsi paru. Pengetahuan tentang manajemen diri yang menentukan kesehatan paru. Tujuan penelitian ini adalah mengetahui pengetahuan kesehatan fungsi paru dalam memprediksi gangguan pernapasan. Desain penelitian adalah *case-control* dari Agustus 2018 hingga Januari 2019. Pengumpulan data dilakukan melalui kuesioner, yaitu kuesioner pengetahuan kesehatan paru yang terdiri atas kategori: faktor risiko, gejala, dan terapi gangguan pernapasan. Sampel penelitian adalah laki-laki dewasa yang bekerja di sektor transportasi di Kota Surabaya dengan menggunakan *purposive sampling*. Analisis data menggunakan *chi-square*. Data yang diperoleh sebanyak 300 orang, terdiri atas 126 orang tanpa gangguan fungsi paru dan 174 orang dengan gangguan fungsi paru. Kategori pengetahuan faktor risiko menunjukkan perbedaan yang bermakna (p=0,000) antarkelompok dengan gangguan terbanyak pada kelompok tingkat rendah (42,0%). Kategori pengetahuan gejala menunjukkan perbedaan yang bermakna (p=0,000) antarkelompok dan sebagian besar kelompok dengan gangguan berada pada kelompok tingkat rendah (55,8%). Kategori pengetahuan gejala pernapasan menunjukkan perbedaan yang bermakna (p=0,000) antarkelompok dengan tingkat pengetahuan keduanya sebagian besar pada tingkat cukup. Oleh karena itu, pengetahuan kesehatan fungsi paru yang rendah mencerminkan kondisi fungsi paru yang rendah.

Kata kunci: Fungsi paru, pengetahuan, perokok

Correspondence: Dr. Amelia Lorensia, S.Farm., M.Farm.Klin., Apt. Department of Clinical-Community Pharmacy, Faculty of Pharmacy, Universitas Surabaya. Jln. Raya Kalirungkut, Surabaya 60293, East Java, Indonesia. E-mail: amelia.lorensia@gmail.com

Introduction

The lungs are the internal organs most susceptible to infection due to the external environment's influence due to constant exposure to particles, chemicals, and organisms in the air. If the respiratory system's primary function does not work properly, there will be a disturbance in the respiratory system.[1] Some examples of respiratory disorders are asthma, sleep apnea, chronic obstructive pulmonary disease (COPD), and lung cancer.[2] Respiratory disease is the leading cause of death and disability in the world. Approximately 65 million people suffer from COPD, and 3 million die each year, making it the third leading cause of death worldwide.[3] In Indonesia, respiratory problems such as lower respiratory tract infections and chronic respiratory diseases are among the top 10 causes of death and have become an economic burden.[4] Respiratory disorders can cause disability and death in almost all world regions, which can occur in all groups of society, especially environmental exposure and poverty, increasing vulnerability to this disease.[3]

The risk factor for smoking is one of the most significant causes of COPD.[5,6] Cigarette smoke also has a high prevalence as a cause of respiratory symptoms and pulmonary function disorders.[7] In developing countries, deaths from COPD have also increased due to the increased number of people who consume cigarettes. In China, smoking causes 12% of mortality and is expected to increase to 30% by 2030. COPD mortality is higher in males and will increase in the >45 years age group due to decreased respiratory function at 30–40 years of age.[8]

In this pandemic, chronic lung diseases (such as COPD, asthma, pulmonary fibrosis, and lung cancer) are at high risk of developing severe conditions if infected with COVID-19. Patients with severe and or uncontrolled asthma/COPD are at a higher risk of more severe COVID-19 infection.[9,10] Smokers who have COPD have a higher risk of developing severe COVID-19 pneumonia than non-smokers. Smoking and vaping are linked to inflammation of the lungs and decreased immune function in the lungs' airways, both of which can increase the likelihood of complications if exposed to COVID-19. Therefore, long-term smokers and e-cigarette users may have a higher risk of developing chronic lung conditions associated with severe cases.[11,12]

Assessment of decreased lung function is necessary to prevent, diagnose, and evaluate various respiratory disorders.[13] Spirometry is the gold standard for examining lung function and is a simple method to measure how a person inhales or exhales.[13] Failure to use appropriate diagnostic tools can further contribute to misjudgment. Although spirometry is an essential tool for diagnosing COPD, it is widely underutilized, even if available in medical practice. A survey of 943 primary care found that, although 64% of practices had access to spirometry, only 34% used it routinely.[14] So this study aims to prove whether the common knowledge assessed by the pulmonary function health knowledge questionnaire can help describe respiratory problems in smokers as someone who is at high risk for decreased lung function. It is because not all people at risk of respiratory problems are aware of the terminology of the disease.[15] Most of them have many misconceptions about respiratory disorders and lack basic knowledge about respiratory disorders.[16,17] Knowledge is essential in the management of a person's illness, self-management in order to avoid disease, and can affect a person's lifestyle.[18,19]

Self-management includes daily activities in which individuals engage and their families, communities, and health care professionals to manage chronic illnesses.[20] Individual self-management can profoundly affect their quality of life and health outcomes. Identifying factors affecting self-management can improve self-management assessments. Inform the development of interventions by identifying potential mediators and moderators of behavior or self-management processes, and help individuals with chronic disease engage in sustainable productive and self-managed processes.[20] Identification of knowledge is also essential as a preventive measure and evaluation of respiratory disorders.[17] Low level of knowledge is related to inappropriate behavioral attitudes in patients with impaired pulmonary function. So that this less specific behavior can reduce lung function, knowledge of pulmonary function health can delay disease progression, improve self-management strategies, and have a better quality of life.[21] The purpose of this study was to identify knowledge of lung function health in predicting respiratory problems in smokers.

Methods

The research design was a case-control study

that was conducted from August 2018 to January 2019. Ethical clearance for this study was obtained from the Institutional Ethical Committee of the University of Surabaya, with certificate No. 034/KE/I/2018. Data was collected through a questionnaire using paper-based, namely a questionnaire on lung function health knowledge. The blueprint for the preparation of the questionnaire can be seen in Table 1. In this study, the variable measured was the knowledge level of respiratory disorders, including risk factors for respiratory disorders,[22–31] symptoms of respiratory disorders,[22,32–34] and treatment/therapy of respiratory disorders;[22,35,36] as well as pulmonary function with an FEV_1/FEC (forced expiration volume in one second/forced vital capacity) assessment.

The population used in the study was male adults. This study involved only the male gender because of differences in stigma and views so that gender can affect knowledge.[37] In addition,

the risk of smoking on respiratory disorders was also influenced by gender.[38] The sample was adult men aged 18–59 years, active smokers, working in the transportation sector, as a public transport driver, and domiciled in Surabaya city, East Java. The sampling technique was purposive sampling.

The questionnaire on lung function health knowledge consisted of three categories: knowledge of risk factors for respiratory disorders, knowledge of respiratory symptoms, and knowledge of respiratory medicine and therapy. First, the correct statement was given a score of 1, while the incorrect was given a score of 0. Then they were assessed and categorized based on the previously calculated cut-off value (Table 2).

The calculations to determine the category of the results of the measurement of knowledge about respiratory symptoms are as follows:[39] good (≥76%), enough (56%), and less (<56%). The data analysis used in this study was a different

Table 1   Blueprint of the Lung Function Health Knowledge Questionnaire

Question Category	Topics	Number	References
Knowledge of risk factors for respiratory disorders	Environmental pollution risk factors	1, 2	22–24
	Risk factors for smoking	3, 4	22, 25, 26
	Work environment risk factors	5, 6	22, 27
	Residence risk factors	7, 8	22, 28
	Age risk factors	9	22, 29
	Risk factors for disease	10, 11	22, 30, 31
Knowledge of respiratory disorders symptoms	Out of breath	1, 2	22, 32
	Chronic cough	3, 4	22, 33
	Wheezing	5	22, 34
	Respiration problems	6	22
Knowledge of treatment and therapy of respiratory disorders	Medical treatment	1, 2, 3	22, 35
	Quit smoking	4, 5	22, 35
	Breathing exercises	6, 7	22
	Physical activity	8	22, 36

Table 2   Classification of Health Knowledge of Lung Function Questionnaire Assessment

Category of Knowledge Question	Number of Questions	Number of Correct Answers for the Knowledge Level Assessment		
		Good	Enough	Less
Risk factors for respiratory disorders	11	9–11	6–8	≤5
Respiratory disorders symptoms	6	5–6	3–4	≤2
Treatment and therapy of respiratory disorders	8	7–8	5–6	≤4

Table 3 Results of the Validity Test of Knowledge of Risk Factors for Respiratory Disorders

Category of Knowledge Question	No.	Question	Corrected Item−Total Correlation	Conclusion
Risk factors for respiratory disorders	1	Highly polluted environments can be at greater risk of respiratory problems.	0.492	Valid
	2	Combustion fumes can cause respiratory problems.	0.665	Valid
	3	Smoking is not a cause of respiratory problems.	0.590	Valid
	4	The more cigarettes smoked, the higher the risk factors for respiratory problems.	0.464	Valid
	5	Working in a dusty environment will not experience respiratory problems.	0.362	Valid
	6	Working in industrial areas has worse lung conditions.	0.452	Valid
	7	Living in a city is more at risk of experiencing respiratory problems than living in a village.	0.664	Valid
	8	Living in industrial areas is more at risk of experiencing respiratory problems.	0.487	Valid
	9	Increasing age does not increase the risk of respiratory problems.	0.469	Valid
	10	Some respiratory diseases can be inherited or passed down from the birth family.	0.431	Valid
	11	A history of respiratory disorders in infants and children can give disability to adulthood.	0.517	Valid
Respiratory disorders symptoms	1	Shortness of breath is not a symptom of respiratory problems.	0.487	Valid
	2	Shortness of breath can get worse during activities.	0.598	Valid
	3	A cough that doesn't go away is a symptom of a respiratory disease.	0.433	Valid
	4	Wheezing (such as a whistling sound or a 'wheezing' sound when breathing in) is a symptom of respiratory disease.	0.621	Valid
	5	Increased breathing rate is not a sign of worsening condition.	0.499	Valid
	6	Increased respiratory rate is often found in patients with respiratory disorders.	0.413	Valid
Treatment and therapy of respiratory disorders	1	Cough symptoms can be reduced with medication (medicine) given.	0.364	Valid
	2	Medications (drugs) are given only to reduce symptoms.	0.408	Valid
	3	Treatment (medicine) given can cure.	0.390	Valid
	4	Quitting smoking does not reduce symptoms.	0.556	Valid
	5	Quitting smoking makes breathing better.	0.366	Valid
	6	Breathing exercises to increase breathing effort.	0.544	Valid
	7	Breathing muscle exercises cannot reduce the symptoms of shortness of breath.	0.683	Valid
	8	Body activity program (sports) to increase tolerance for physical activity.	0.362	Valid

test of the two groups with the chi-square test to determine the differences between the groups with and without pulmonary function disorders.

Results

The subject was 30 people residing in Surabaya city. Validity and reliability tests were carried out using SPSS for Windows version 24. The validity test results of the knowledge of the risk factors for respiratory disorders showed that all questions from the three categories were valid. The questionnaire is valid if r count>table (r tabel=0.361), and Table 3 shows that the table value for 30 respondents has a value above the table value. The reliability test results were

Table 4 Knowledge Reliability Test Results of Risk Factors for Respiratory Disorders

Category of Knowledge	Reliability Statistic	
	Cronbach's Alpha	N of Item
Risk factors for respiratory disorders	0.719	11
Respiratory disorders symptoms	0.604	6
Treatment and therapy of respiratory disorders	0.672	8

Table 5 Frequency Distribution of Respondent Characteristics

Respondent Characteristics	Division of Groups based on Lung Function			
	No Impaired Lung Function (n=126)		Impaired Lung Function (n=174)	
	Frequency	%	Frequency	%
Age (years)				
Late adolescence (15–25)	0	0.0	2	1.1
Early adulthood (26–35)	5	4.0	9	5.2
Late adulthood (36-45)	58	46.0	19	10.9
Early elderly (46–55)	43	34.1	52	29.9
Late elderly (56–65)	20	15.8	25	14.4
Level of education				
No school	15	11.9	35	20.1
Kindergarten	0	0.0	2	1.2
Elementary school	58	46.0	104	59.8
Junior high school	19	15.1	19	10.9
Senior high school	34	27.0	14	8.1
BMI (kg/m^2)[40]				
Thin	15	11.9	11	6.3
Normal	87	69.0	127	73.0
Overweight	19	15.1	22	12.7
Obesity	5	4.0	11	6.3
History of disease				
Diabetes	0	0.0	4	2.3
Hyperuricemia	0	0.0	3	1.7
Hypertension	0	0.0	4	2.3
Dyslipidemia	0	0.0	3	1.7
Don't know/don't exist	126	100.0	159	91.4
Lung fungtion value (FEV^1/FVC) (%)[22]				
No decrease (≥80)	126	100.0	0	0.0
Decrease mild level (65–<80)	0	0.0	76	43.7
Decrease moderate level (50–<65)	0	0.0	94	54.0
Decrease severe level (<50)	0	0.0	4	2.3

declared reliable because they had Cronbach alpha values between 0.61–0.80 (Table 4).

The data obtained in the study were 300 people consisting of 126 people who did not experience lung function problems and 174 people who had lung function disorders. Based on the frequency of respondent characteristics, the age category in the respondent's group without pulmonary function disorders was mostly in late adulthood 36–45 years (46.0%), and those with pulmonary function disorders were most in early elderly 46–55 years (29.9%). In the education level category, elementary school education level was the highest in the two groups. In the body mass index (BMI) category,[40] respondents had normal BMI in both groups (Table 5).

Table 6 shows categories of the knowledge level of lung function health. The knowledge level of lung function health in the knowledge category of risk factors for respiratory disorders showed a significant difference (p=0.000) between the groups without pulmonary function disorders and lung function disorders. Most of the groups with impaired lung function were at the low knowledge level (42.0%). Whereas without any disruption in lung function, most of them were at a sufficient knowledge level (50.0%). In the category of knowledge of respiratory symptoms, there was a significant difference (p=0.000) between the groups without pulmonary function disorders and those with pulmonary function disorders. Most of the groups with impaired lung function were at a low knowledge level (55.8%). Whereas without any disruption in lung function, most of them were at a sufficient knowledge level (50.0%). In the category of knowledge of respiratory symptoms, there was a significant difference (p=0.000) between the groups without pulmonary function disorders and those with lung function disorders, with the knowledge level in the two groups most at the sufficient knowledge level.

Discussion

This study involved respondents with active smokers because many young people smoke, and the prevalence of smokers is increasing from year to year. Indonesia is also the third-largest cigarette consumer in the world.[41] Previous studies related to respiratory diseases and smoking had discussed the effect of smoking on the health of lung function,[42–44] related to the economy,[45] or smoking cessation.[46] In Indonesia, similar studies on the knowledge level of lung function health in smokers, such as the level of danger of smoking,[47] impact oral health,[48] are generally carried out at young ages and students. However, similar research on public transport drivers does not yet exist, and what exists is a picture of food intake, such as rickshaw drivers.[49]

The risk factor for smoking is one of the most significant influential causes of COPD.[50] Cigarette smoke also has a high prevalence as a cause of respiratory symptoms and pulmonary function disorders.[51] Assessment of decreased lung function uses a lung function test, an objective measurement of whether a person's lung function is normal or abnormal. Pulmonary function tests are usually performed based on specific indications or needs. Pulmonary function tests were carried out by assessing the function

Table 6 Categories of the Knowledge Level of Lung Function Health

Category	Knowledge Level	Division of Groups based on Lung Function				p Value[*]
		No Impaired Lung Function (n=126)		Impaired Lung Function (n=174)		
		Frequency	%	Frequency	%	
Risk factors for respiratory disorders	Good	20	15.9	38	21.8	0.000
	Enough	63	50.0	63	36.2	
	Less	43	34.1	73	42.0	
Respiratory disorders symptoms	Good	39	31.0	13	7.5	0.000
	Enough	63	50.0	64	36.8	
	Less	24	19.0	97	55.7	
Treatment and therapy of respiratory disorders	Good	39	31.0	13	7.5	0.000
	Enough	63	50.0	64	36.8	
	Less	24	19.0	97	55.7	

Note: [*]chi-square test

of ventilation, gas diffusion, pulmonary blood perfusion, and transport of O_2 and CO_2 gases in the blood.[21] Usually, assessing a person's lung function is sufficient to perform the FEV_1 pulmonary ventilation function test. Ventilatory function with good value can represent the overall lung function, and usually, other lung functions are also good. Assessment of ventilation function is closely related to the assessment of respiratory mechanics. A spirometer is used to assess the function of ventilation and record a graph of breathing based on the amount and velocity of air that is exited or entered into the spirometer.[21] In the study, pulmonary function tests were performed using a hand-held spirometer-type spirometry device. Spirometry was chosen because spirometry is the gold standard for examining lung function and is a simple method that can measure how a person inhales or exhales.[22]

Factors affecting lung function apart from knowledge include age, sex, height, weight, sex, and race.[52] Changes in the structure of the lungs are mainly associated with an increase in the size of the alveolar space without inflammation or damage to the alveolar wall, which is called senile emphysema. This microscopic emphysema increases linearly with increasing age in nonsmokers, but in smokers, a more progressive increase in alveolar space size can only be observed in specific (susceptible) individuals. Senile emphysema can be a consequence of the loss of the supporting structures of the lung parenchyma. Moreover, it has been observed that the elasticity of the lungs decreases with age. It has been postulated that this phenomenon is due more to the reduced surface tension force of the alveoli due to an increase in the size of the individual diameter compared to changes in elastin and collagen in the pulmonary parenchyma.[53]

Body mass index is often defined as body weight (kilograms) divided by height (meters) squared (kg/m^2). BMI is related to body fat, which can categorize obesity and malnutrition in both adults and children. BMI is also used to assess nutritional deficiency, where a BMI<18.5 kg/m^2 indicates nutritional deficiency. Malnutrition in COPD is associated with complications and increased mortality. COPD patients with low body weight have a lower diffusion capacity and exercise than normal-weight COPD patients. Reduced body cell mass is associated with reduced

diaphragm mass and respiratory muscle mass. Malnutrition is also associated with decreased immune status, so that unwanted complications can occur, such as nosocomial lung infections and hypercapnic lung failure.[54]

A limitation in this study was that this study does not assess the severity of smoking which can affect respiratory symptoms and pulmonary function disorders.[7] Examination of lung function uses a type of hand-held spirometers, a type of spirometry that was easy and affordable. However, they differ in values from more accurate spirometry types such as bellows spirometer or rolling seal.

Conclusions

The knowledge level of lung function health, there were differences in the knowledge category of risk factors for respiratory disorders, symptoms of respiratory disorders, and treatment and therapy of respiratory disorders between groups without lung function disorders and with impaired lung function. Suggestions for future research are to increase the assessment of risk factors that can affect lung function. In addition, it is necessary to carry out similar research on respondents with different characters, such as different occupations that are at risk of exposure to respiratory problems (construction workers, mining workers, parking attendants), or differences in education, gender, and e-cigarette smokers.

Conflict of Interest

All authors stated that there was no conflict of interest in this study.

Acknowledgments

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RESEARCH ARTICLE

Thirdhand Smoke Exposure in Mice Pancreas Microstructure

Eva Rianti Indrasari,[1] Annisa Rahmah Furqaani,[2] Listya Hanum Siswanti,[3] Ihsan Muhammad Nauval,[4] Putra Zam Zam Rachmatullah[4]

[1]Department of Biochemistry, Nutrition, and Biomolecular, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia, [2]Department of Medical Biology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia, [3]Department of Histology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia, [4]Medical Undergraduate Study Program, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

Cigarette residue toxins can accumulate in the body, including the pancreas, which potentially reduces pancreas function. In addition, the active compounds in cigarettes are reporting to interfere with an elevation of reactive oxygen species, leading to disruption of pancreatic microstructures. Furthermore, pancreatic cell dysfunction is responsible for developing diabetes mellitus disease. The objective of this study was to analyze the effect of thirdhand smoke exposure on mice pancreatic microstructure image. It was an in vivo laboratory experimental study with a completely randomized design at the Medical Biology Laboratory of the Universitas Islam Bandung from November 2020–June 2021. The subjects were 20 adult male mice aged 8–10 weeks, weighing 25–30 grams, in good health condition, and randomly divided into two groups (control group and treatment group exposed to thirdhand cigarette smoke for four weeks). After the completion of the exposure period, pancreatic cells isolation was performing. The parameters observed in this study were the number and diameter islet of Langerhans. Data analysis used the independent t test parametric (α=5%). The results showed that the number and diameter islet of Langerhans in the treated group were significantly lower than the control group (p<0.05). The average number in the control group was 9.40±3.20, while in the treatment group was 4.90±2.74 (28% smaller). The average diameter of control was 225.96±50.15 mm, while treatment was 162±49.68 mm (50% lower). In conclusion, thirdhand smoke exposure alters the pancreas microstructure. The toxic compounds on thirdhand cigarette smoke are involving in generating an elevation of free radical levels, depletion of antioxidants, and alteration of signal transduction resulted in acceleration of apoptosis rate of the islet of Langerhans, especially pancreatic β-cells.

Keywords: Pancreas microstructure; pancreatic β-cells, thirdhand smoke

Pengaruh Paparan Asap Rokok Tersier pada Gambaran Mikrostruktur Pankreas Mencit

Abstrak

Toksik residu rokok dapat terakumulasi pada tubuh, termasuk pankeas sehingga dapat menurunkan fungsi pankreas. Selain itu, senyawa aktif dalam rokok dilaporkan meningkatkan radikal bebas yang menyebabkan kerusakan mikrostruktur pankreas. Selanjutnya, disfungsi sel pankreas meningkatkan risiko diabetes melitus. Penelitian ini bertujuan menganalisis pengaruh asap rokok tersier terhadap gambaran mikrostruktur pankreas mencit. Penelitian ini merupakan penelitian eksperimental laboratorium in vivo dengan rancangan acak lengkap di Laboratorium Biologi Medik Universitas Islam Bandung periode November 2020–Juni 2021. Subjek penelitian adalah 20 mencit jantan dewasa berumur 8–10 minggu, bobot 25–30 gram, kondisi sehat, dan dibagi secara acak menjadi dua kelompok (kelompok kontrol dan kelompok perlakuan yang mendapat paparan asap rokok tersier selama empat minggu). Setelah periode pemberian paparan selesai, dilakukan isolasi sel pankreas. Parameter yang diamati dalam penelitian ini adalah jumlah dan diameter pulau Langerhans (*islet of Langerhans*). Analisis data menggunakan parametrik *independent t test* (α=5%). Hasil penelitian menunjukkan bahwa jumlah dan diameter pulau Langerhans pada kelompok perlakuan lebih rendah dibanding dengan kelompok kontrol (p<0,05). Jumlah rerata pada kelompok kontrol adalah 9,40±3,20, sedangkan pada kelompok perlakuan 4,90±2,74 (28% lebih rendah). Diameter rerata pada kelompok kontrol adalah 225,96±50,19 mm dan kelompok perlakuan 162,89±49,68 mm (50% lebih rendah). Simpulan, paparan asap rokok tersier dapat memengaruhi gambaran mikrostruktur pankreas. Senyawa toksik pada asap rokok tersier diduga terlibat dalam peningkatan kadar radikal bebas, penurunan kadar antioksidan, dan perubahan transduksi sinyal yang mengakibatkan peningkatan laju apoptosis pulau Langerhans, terutama sel β pankreas.

Kata kunci: Asap rokok tersier, mikrostruktur pankreas, sel β pankreas

Correspondence: Eva Rianti Indrasari, dr., M.Kes. Department of Biochemistry, Nutrition, and Biomolecular, Faculty of Medicine, Universitas Islam Bandung. Jln. Tamansari No.22, Bandung 40116, West Java, Indonesia. E-mail: evaindrasariMD@gmail.com

Introduction

The concerns of tobacco smoking hazards are increasing due to the magnitude of public health threats posed by the chemical cessations. Toxic, mutagenic, and carcinogenic compounds were formed because of the chemical reaction between smoke residues exhaled from active smokers with chemical compounds in the air. The residues remain in the various surfaces of objects for a long period.[1,2]

Admittedly, cigarette residue, tertiary cigarette smoke, or thirdhand smoke (THS) left in the environment or on the surface of objects is as dangerous as primary and secondary cigarette smoke. About 50% of the nicotine left on the clothing or skin is dissolved by sweat and absorbed into the body through the skin. Nicotine reacts with oxygen and nitrogen in free air, producing tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs). Those substances can be unstable compounds at high temperatures and mutagenic. They are also carcinogenic. These compounds can be used as markers for the presence of THS or cigarette residues.[1–3]

Consequently, chronic exposure to THS may lead to many cellular metabolism alterations. In human bronchial epithelial cells, DNA damage from oxidative stress provoked by THS results in alveolar thickening, uncontrolled cell growth, and tumor formation.[3,4] Not only affecting lung cells, but exposure to THS in mice is also related to a disturbance in glucose and fat metabolism, increased proinflammatory cytokines, and fat deposition in the liver.[5,6] Thus, the condition can contribute to disruptions of hepatic metabolism interfered with the signal transduction of pancreatic cells, leading to diabetes mellitus type 2 in mice fetuses.[7,8]

Although THS is known to increase the risk of many diseases, the specific effects of prolonged exposure to certain organs are still debatable. In addition, there were limited resources and researches on the mechanism of THS in causing pathological conditions in nonsmokers. Therefore, the objective of this study was to analyze the effect of THS exposure on the mice's pancreas microstructure.

Methods

This was an in vivo laboratory experimental study with a completely randomized design. The subjects were 20 adult male mice aged 8–10 weeks, weighing 25–30 grams, in healthy condition, no injuries, active, and responsive. The experimental animals were randomly divided into two groups, the control and treatment groups.

The research was conducted from November 2020 to June 2021. The locations of all stages of the study were at the Medical Biology Laboratory of the Bandung Islamic University. All the experimental animals which met inclusion criteria were adapted to the research conditions (acclimatization) for one week. During the research period, the experimental animals were caged in plastic tubs measuring 28×34×14 cm— each cage filled with five experimental animals. The treatment group received TSH exposure for four weeks.

Exposure to tertiary cigarette smoke was carried out by fumigating the experimental animal cages with cigarettes. In the process of fumigating the pen, the experimental animals were transferred to another cell and carried out in a different place from the experimental animal rearing area so that the experimental animals were not exposed to cigarette smoke directly. One cigarette was entirely burned for about one hour, and the smoke was allowed to surround the cages of the treated mice. The cell was covered with a plastic cover during fumigation. It was done every day for four weeks.

After exposure period completion, animals were sacrificed by cervical dislocation, and the pancreas was isolated. Then it was fixed with 10% formalin buffer, impregnated into the paraffin block. Furthermore, the tissue on the paraffin block that had been cut was glued to the slide and stained with Harris hematoxylin-eosin (HE) staining. The microscopic slides were then observed using a microscope connected to a computer equipped with Optilab Viewer and Raster Image software. The number and diameter islets of Langerhans were analyzed. At the end of the study, all experimental animals left were sacrificed, and the body parts of mice that were not used in the study were collected and buried. Data analysis was performed using an independent t test (α=5%).

This study has obtained ethical approval from the Health Research Ethics Committee of the Universitas Islam Bandung with approval number: 111/KEPK-Unisba/XI/2020.

Results

The data obtained in this study were the number and diameter islet of Langerhans and are listed in Table. The data in Table shows that THS exposure altered the islet of Langerhans in the pancreas. The differences were seen from two histological parameters, the number, and diameter of each islet. The treatment group was smaller in diameter and lesser amount of cells compared with the control group. The difference of two parameters observed in the two groups showed significant results statistically (p<0.05). The average number of islet of Langerhans in the treatment group was almost 50% less than in control. Likewise, the diameter islet of Langerhans in the treatment group was 28% smaller than that control. These results suggest that THS exposure afflicted the microstructure of the pancreas in experimental animals.

Figure shows a histopathological description of the microstructure of the pancreas. The images are taken from sizes that represent the average diameter of each group. There were differences in histopathological features between the two groups, where the group exposed to tertiary cigarette smoke showed lower cell density and smaller diameter than the control group.

Discussion

Cigarette smoke residue that is left in the room still contains active ingredients that can last for months after cigarette smoke is diminished. Furthermore, they generally form new compounds after reacting with the surrounding

Table Number and Diameter Islet of Langerhans Observation

Parameters	Groups		p Value*
	Control (n=10)	Treatment (n=10)	
Average number islet (mean±SD)	9.40±3.20	4.90±2.74	0.005
Average diameter islet (mm) (mean±SD)	225.96±50.19	162.89±49.68	0.015

Note: *independent t test, p<0.05 significant
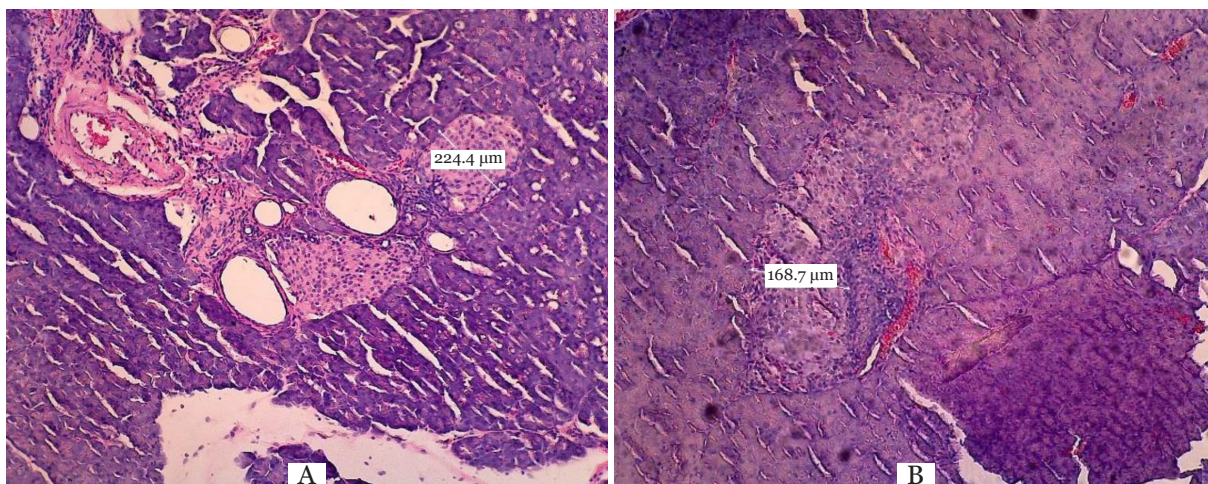
Figure Observation of the Microstructure of the Pancreas between Control and Treatment Group

(**A**) Histopathological microstructure of the pancreas and islets of Langerhans in the control group. The diameter appeared to be larger, and the islet of Langerhans appears to be denser than the treatment group (B). (**B**) Histopathological microstructure of the pancreas and islet of Langerhans in the treatment group. The mean diameter of islet cells of Langerhans appears to be smaller, and the density of the cells is lower than the control group

environment.

According to the results of this study, it has been shown that THS exposure in experimental animals affects pancreas microstructure. Previous studies have reported a significant association between smoking and the incidence of pancreas damage. Several theories discuss mechanisms of pancreatic damage caused by smoking, for instance, the elevation of oxidative stress and lipid oxidation induced by the active compound in cigarettes, nicotine.[9] Other studies have reported that active substances in cigarettes can increase caspase-3, hypoxia-inducible factor-1 (Hif-1), Hif-2, calcitonin gene-related protein (CGRP), and TNF-α expression in the pancreas. Caspase-3 is an inactive proenzyme in the cytosol, which, when activated, can induce apoptosis. Increased activation of caspase-3 after exposure to cigarette smoke was the cause of pancreatic cell apoptosis. Exposure to cigarette smoke is also associated with increased expression of a transcription factor induced in chronic hypoxic and inflammatory conditions, hypoxia-inducible factors (Hifs). Increased Hif-1 and Hif-2 is a sign of hypoxia, and chronic inflammation has occurred in pancreatic cells exposed to cigarette smoke.[10] Other proteins found to increase in pancreatic cells after exposure to cigarette smoke is CGRP-related peptide amylin. This expression of pancreatic CGRP decreases insulin release from pancreatic β-cells, causing hyperglycemia. CGRP also mediates the insulin resistance mechanism in skeletal muscles, thereby increasing the risk of diabetes mellitus.[11]

Adhami et al.[12] reported elevation of peripheral reactive oxygen species in mice exposed to THS and significantly decreased activity and cellular antioxidant ratio. THS toxins also disrupt the endoplasmic reticulum of pancreatic cells by causing ER stress, causing lipid, protein, and DNA damage. Consequently, the situation leads to cellular and molecular damage of pancreatic cells and insulin signaling. As a result, Mice exposed to THS had hyperglycemia, hyperinsulinemia, and a higher insulin resistance index than the control group.

Cadmium (Cd) is one of the main components of cigarette smoke. In vivo studies reported Cd exposure is related to the impairment of blood glucose regulation and islet of Langerhans dysfunction. Animal studies have shown that Cd can cause damage to pancreatic β-cells, suppress insulin secretion, increase glucose intolerance,

and have a diabetogenic effect. Exposure to these compounds in the subchronic or chronic period leads to impaired glucose homeostasis, islets of Langerhans damage, lower levels of insulin secretion, and elevated gluconeogenic enzymes.[13]

Cd accumulation in blood and pancreas causing suppression of insulin secretion and apoptosis of pancreatic β-cells by inducing oxidative cellular damage in vivo and in vitro. The mitochondria of β-cells can produce excessive levels of reactive oxygen species (ROS), and they are both a major source of ROS in these cells and are also prime targets for ROS attack. Therefore pancreatic β-cells have a greater risk of developing apoptosis due to ROS attack than other cell types. When combined with the failure of the ROS defense system, these conditions can result in a relatively high susceptibility of β-cells to oxidative stress damage.[13,14]

Chang et al.[14] reported that cadmium-associated pancreatic β-cells damage correlates with aggravation of oxidative stress and alteration in intracellular signaling. Additionally, Cd exposure is also responsible for elevated malonaldehyde levels in the plasma and pancreatic cell membranes of experimental animals. Malonaldehyde is an aldehyde compound which is acts as a marker of oxidative stress in cells. Furthermore, Cd-induced altered the expression of matrix metalloproteinase (MMP) and increasing the release of cytochrome c from the mitochondria to the cytosol. Chang also highlighted the elevated levels of Cd in beta pancreas cells caused phosphorylation of c-jun N-terminal kinases (JNK). This protein mediates cell survival or apoptosis (depends on the stimuli). Accordingly, the intracellular elevation of cadmium level suspected to cause apoptosis in pancreatic β-cells.

The other main cigarette compound is nicotine. Nicotine has an essential role in enhancing premature senescence of β-cells in diabetes model mice after 12h of nicotine in drinking water. Moreover, it increases intracellular Ca^{2+} and reactive oxygen species (ROS), which leads to further damage of β-cells after 28 days of administration. In consequence, nicotine leads to the destruction of pancreatic β-cells.[15]

Another study reported short-term exposure to a nicotine concentration of more than one μ mol/L in 48 hours inhibits insulin release. These findings indicate that pancreatic islets and β-cells had been affected in such short periods

of exposure. Other studies have shown nicotine exposure can lead to β-cell dysfunction, increased β-cell apoptosis, and loss of β-cells chained via mitochondrial and related pathways.[16]

Tong et al.[17] proclaimed that cigarette smoking in high-fat diet mice correlated with disruption of endoplasmic reticulum through the elevation of ceramide in β-cells compared to the non-smoking group. Admittedly, β-cells in mice with cigarette smoking treatment also exhibits deflated proliferation and had lower mass cells after 22 weeks of treatment.

The results of this study have corresponded to the effect of cigarette smoke or cigarette residues on the pancreas. The decrease in the number and diameter of islet of Langerhans is thought to be an indicator of the toxicity effect of THS exposure. Changes in the pancreas microstructure cause elevated levels of ROS, depleted of antioxidant activity, and increase the level of inflammatory cytokines and transcriptions factors such as active caspase-3, CGRP, TNF-α, Hif-1, Hif-2. It also increases intracellular Ca^{2+}. In this case, a decrease in the number and diameter of the isle of Langerhans. A reduction in number and diameter is thought to be involved in causing a decrease in pancreas ability of the pancreas to regulate or maintain blood glucose homeostasis.[18] Dai et al.[19] states that heavy metals contained in cigarettes include cadmium (Cd) and lead (Pb). Cadmium has a long half-life in the human body (20–40 years); hence, it can accumulate in the body and potentially activate the oxidative stress mechanism, resulting in an elevated level of free radicals. The enhancement of free radicals is positively correlated with DNA fragmentation which triggers DNA damage.

Furthermore, the accumulation of Cd in pancreatic islets potentially damages cells in the islet. It alters islet function that contributes to Cd-induced hyperglycemia.[20] Another study declared that indirect exposure of nicotine to gestating mice provoked the reduction of GLUT4 expression in the muscle's offspring. Likewise, observation of pancreatic islets in this treatment group showed lower PDX-1 expression in male offspring while females had higher PDX-1, GLUT2 expressions, and lower α2 adrenergic receptors. These results suggested that maternal exposure to nicotine affects glycemic homeostasis and peripheral insulin signaling in offspring, thus increasing the risk for type 2 diabetes development.[21] Studies have already shown that cigarette smoke causes dysfunction in pancreatic β-cells and impairs insulin production.

Nevertheless, the exact mechanisms remain unclear. Sun et al.[22] demonstrated that cigarette smoke extract inhibits insulin production by upregulating thioredoxin-interacting protein via metastasis-associated lung adenocarcinoma transcript-1 (MALAT1)-mediated downregulation of microRNA (miR-17). This mechanism is involved in the reduced β-cells function. The sera of diabetic patients who smoked had higher MALAT1 levels and lowered miR-17 levels than nonsmokers' sera. Cigarette smoking increases the risk of type 2 diabetes through oxidative stress mechanisms. Oba et al.[23] showed that cigarette smoking affects insulin sensitivity in Asian populations, especially the Japanese. The intensity of smoking (number and or frequency) in both active and passive smoking appears to be associated with diabetic states, including impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Even though the study showed that no significant association was observed with a homeostatic model assessment of insulin resistance (HOMA-IR) in Japanese subjects, suggesting that races may influence the glucose metabolism of smoking people. Pancreatic cancer (PaCa) risk was also associated with smoking. The possible mechanism link might be the accumulation of advanced glycation end-products (AGEs). AGE N^{ε}-carboxymethyl lysine (CML) in human pancreatic ductal adenocarcinoma (PDA) cell lines promoted PDA cell growth and receptor for AGEs (RAGE) expression. In addition, they activated downstream tumourigenic signaling pathways.[24,25] The results of this study are in line with previous research that cigarette smoke exposure may affect the structure of the pancreas and contribute to disrupting pancreatic function.

Conclusions

The results presented that thirdhand smoke exposure alters the pancreas microstructure. The toxic compounds on thirdhand cigarette smoke are involving in generating an elevation of free radical levels, depletion of antioxidants, and alteration of signal transduction resulted in acceleration of apoptosis rate of the islet of Langerhans, especially pancreatic β-cells.

Conflict of Interest

The authors have no conflict of interest to declare.

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RESEARCH ARTICLE

Activity of Javanese Ginger, Turmeric, Garlic, and Pomegranate Flower on LDL-C and Total-C on Dyslipidemia Model Rats

Larissa,[1] Penny Setyawati Martioso,[1] Diana Krisanti Jasaputra[2]
[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia,
[2]Department of Pharmacology, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia

Abstract

High levels of LDL cholesterol are risk factors for coronary heart disease. Different types of medicinal plants have hypolipidemic effects. The study aimed to compare the potential of Javanese ginger ethanol extract, turmeric, garlic, and pomegranate flowers with rosuvastatin on levels of LDL cholesterol (LDL-C) and total cholesterol (total-C) male Wistar rats dyslipidemia models. This experimental laboratory research was conducted in Maranatha Animal Research Laboratory Bandung and was carried out in January–December 2020. The experimental animals were divided into six groups (n=5): the control group, the Javanese ginger group, the turmeric group, the garlic group, the pomegranate flower group, and the comparison control group. The induction given to experimental animals was administering vitamin D3, a high-fat diet, and propylthiouracil for 14 days. The results showed that the administration of 175 mg/kg BW of garlic ethanol extract (−44.85%), pomegranate flowers (−58.74%), and rosuvastatin (−40.00%) reduced LDL-C compared to control (p<0.05). The administration of 175 mg/kg BW of Javanese ginger ethanol extract (−15.16%), turmeric (−14.02%), garlic (−22.80%), pomegranate flower (−65.24%), and rosuvastatin (−18.70%) reduced total-C compared to controls (p<0.05). The conclusion is that garlic and pomegranate flowers lowered LDL-C, while Javanese ginger, turmeric, garlic, and pomegranate flowers reduced total-C.

Keywords: Garlic, Javanese ginger, LDL-C, pomegranate flower, total-C, turmeric

Aktivitas Temulawak, Kunyit, Bawang Putih, dan Bunga Delima terhadap K-LDL dan K-Total pada Tikus Model Dislipidemia

Abstrak

Kadar kolesterol LDL yang tinggi adalah faktor risiko penyakit jantung koroner. Berbagai jenis tanaman obat memiliki efek hipolipidemik. Penelitian ini bertujuan membandingkan potensi ekstrak etanol temulawak, kunyit, bawang putih, dan bunga delima dengan rosuvastatin pada kadar kolesterol LDL (K-LDL) dan kolesterol total (K-total) tikus Wistar jantan model dislipidemia. Penelitian laboratorium eksperimental ini dilakukan di Laboratorium Penelitian Hewan Maranatha Bandung dan dilakukan pada Januari–Desember 2020. Hewan coba dibagi menjadi enam kelompok (n=5), yaitu kelompok kontrol, kelompok temulawak, kelompok kunyit, kelompok bawang putih, kelompok bunga delima, dan kelompok pembanding. Induksi yang diberikan kepada hewan coba adalah pemberian vitamin D3, pakan lemak tinggi, dan *propyltiouracil* selama 14 hari. Hasil penelitian menunjukkan bahwa pemberian 175 mg/kgBB ekstrak etanol bawang putih (−44,85%), bunga delima (−58,74%), dan rosuvastatin (−40,00%) mengurangi K-LDL dibanding dengan kontrol (p<0,05). Pemberian 175 mg/kgBB ekstrak etanol temulawak (−15,16%), kunyit (−14,02%), bawang putih (−22,80%), bunga delima (−65,24%), dan rosuvastatin (−18.70%) mengurangi K-total dibanding dengan kontrol (p<0,05). Kesimpulannya, bunga bawang putih dan delima menurunkan K-LDL, sedangkan temulawak, kunyit, bawang putih, dan bunga delima menurunkan K-total.

Kata kunci: Bawang putih, bunga delima, K-LDL, K-total, kunyit, temulawak

Introduction

The number one cause of death in the world, according to WHO, is cardiovascular disease which causes the death of 17.9 million people each year. Cardiovascular diseases include coronary heart disease, blood vessel disease, and stroke.[1] Cardiovascular disease occurs because of the atherosclerosis process. The process of atherosclerosis begins with the formation of plaque on the walls of blood vessels. This plaque can grow to be large and cause narrowing of the arteries and cause blockage. Blockage of these blood vessels can cause a heart attack or stroke. Cardiovascular disease has several risk factors, non-modifiable risk factors, and modifiable risk factors. Non-modifiable risk factors for cardiovascular disease that cannot change include genetics and previous disease history. The other side modifiable risk factors can be changed, such as lipid profile levels, blood glucose levels, obesity, smoking habits, and high blood pressure. Several studies have shown hypercholesterolemia, and elevated LDL cholesterol (LDL-C) levels have shown a positive correlation with an increased risk of coronary heart disease.

Coronary heart disease (CHD) and stroke are estimated to cause more than 470,000 deaths each year in Indonesia. The five main risk factors that can be changed are smoking, hypertension, diabetes, increased total cholesterol (total-C), and being overweight.[2] Dyslipidemia is a major risk factor for coronary heart disease in a patient with type 2 diabetes. Dyslipidemia includes an increase in LDL-C and total-C. The drugs such as statins are directly associated with a reduced risk of cardiovascular disease.[3]

Traditional Indonesian medicines can overcome hypercholesterolemia, including *Guazuma ulmifolia* leaves, *Cassia senna* leaves, *Sonchus arvensis* leaves, *Camellia sinensis* leaves, *Curcuma xanthorrhiza* rhizomes, *Curcuma longa* rhizomes, and *Phyllanthus niruri*.[4] Some other agents used to inhibit cholesterol increase include rice bran, dragon fruit, soy powder, and oyster mushrooms.[5–7] In addition, traditional medicines that can be used for hypercholesterolemia are garlic and pomegranate flowers.

The study aimed to compare the potential of Javanese ginger ethanol extract, turmeric, garlic, and pomegranate flowers with rosuvastatin on levels of LDL cholesterol (LDL-C) and total cholesterol (total-C) male Wistar rats

dyslipidemia models.

Methods

This study used male Wistar rats aged eight weeks with an average body weight of 150–200 grams obtained from the Faculty of Pharmacy Science and Technology, Institut Teknologi Bandung. The research was conducted in January–December 2020 at the Maranatha Animal Research Laboratory, Bandung. The Research Ethics Committee of the Faculty of Medicine, Universitas Kristen Maranatha Bandung, approved the study (Protocol Number: 144/KEP/X/2020).

This experimental laboratory research design used a randomized control group with male Wistar rats divided into six groups (n=5). In addition, groups were divided into control groups, the Javanese ginger ethanol extract group, the turmeric ethanol extract group, the garlic ethanol extract group, pomegranate flowers, and the comparator control group. The data measured were LDL-C levels and total-C levels in the treatment group and were analyzed using the one-way ANOVA analysis method and LSD test with alpha=0.05.

The experimental animals were adapted for seven days and then induced single-dose vitamin D3 140,000 IU/200 g orally before intervention with standard feeding and distilled water ad libitum.[8] The experimental animals were given high-fat feed (HFF) and drinking water with 0.01% propylthiouracil (PTU) for 14 days. The experimental animals were randomly assigned to six groups (n=5) with 14 days of treatment. Each treatment was given with a volume of 2 mL orally using an oral sonde: Group 1: given CMC 1% and HFF and water with 0.01% PTU for 14 days; Group 2: Javanese ginger ethanol extract at a dose of 175 mg/kg BW orally and HFF and water with 0.01% PTU for 14 days; Group 3: 175 mg/kg BW turmeric ethanol extract orally, HFF, and water with 0.01% PTU for 14 days; Group 4: 175 mg/kg BW garlic ethanol extract orally, HFF and water with 0.01% PTU for 14 days; Group 5: 175 mg/kg BW pomegranate flower ethanol extract of dose of orally, HFF, and water with 0.01% PTU for 14 days; and Group 6: rosuvastatin orally and PLT with water with 0.01% PTU for 14 days.

On the fifteenth day, after receiving treatment for 14 days, blood serum was taken from the infraorbital veins.

Results

The results in the form of LDL-C levels after 14 days of treatment were presented in Figure 1. Data on the percentage reduction in LDL-C in the treatment group were tested by one-way ANOVA and obtained a p value<0.05. It means that at least there was a pair of treatment groups that have a significant difference.

Table 1 showed that garlic (−44.85%) and pomegranate flowers (−58.74%) lowered LDL-C compared to the control with a significant difference. The potential of pomegranate flowers (−58.74%) in lowering LDL-C was better than rosuvastatin (−40.00%), while the potential of garlic (−44.85%) was equivalent to rosuvastatin which was used as a comparison.

The results in the form of total-C levels after 14 days of treatment were presented in Figure 2. Data on the percentage reduction in total cholesterol in the treatment group were tested by one way ANOVA and obtained a p value<0.05. It means that at least there was a pair of treatment groups that have a significant difference.

Table 2 showed that Javanese ginger (−15.16%), turmeric (−14.02%), garlic (−22.80%), and pomegranate flowers (−65.24%) reduced total-C compared to controls with significant differences. The potential of garlic (−22.80%) and pomegranate flowers (−65.24%) in lowering total-C were better than rosuvastatin (−18.70%), while the potential for Javanese ginger (−15.16%) and turmeric (−14.02 %) equivalent to rosuvastatin which was used as a comparison.
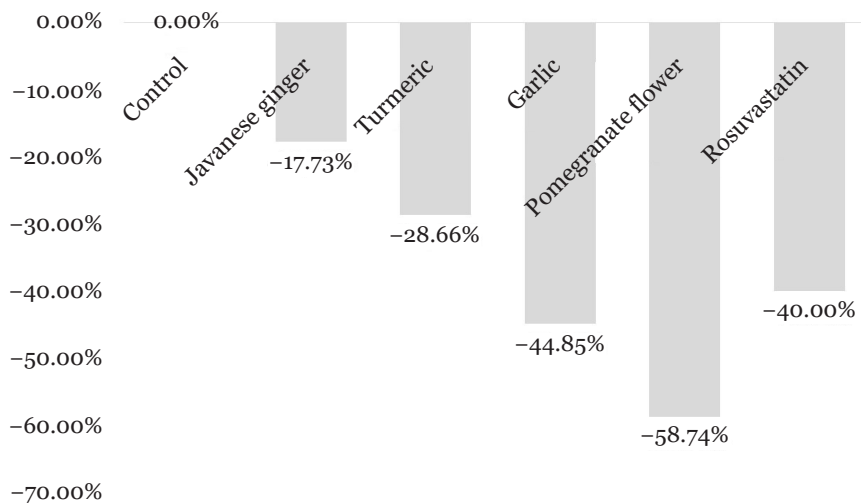
Figure 1 Percentage Reduction in LDL-C Compared to Controls

Table 1 LSD Test Results in Lowering LDL-C Data of the Six Treatment Group

	Control	Javanese Ginger	Turmeric	Garlic	Pomegranate Flower	Rosuvastatin
	0.00%	**−17.73%**	**−28.66%**	**−44.85%**	**−58.74%**	**−40.00%**
Control		NS	NS	**	**	**
Javanese ginger			NS	**	**	**
Turmeric				**	**	**
Garlic					NS	NS
Pomegranate flower						*
Rosuvastatin						
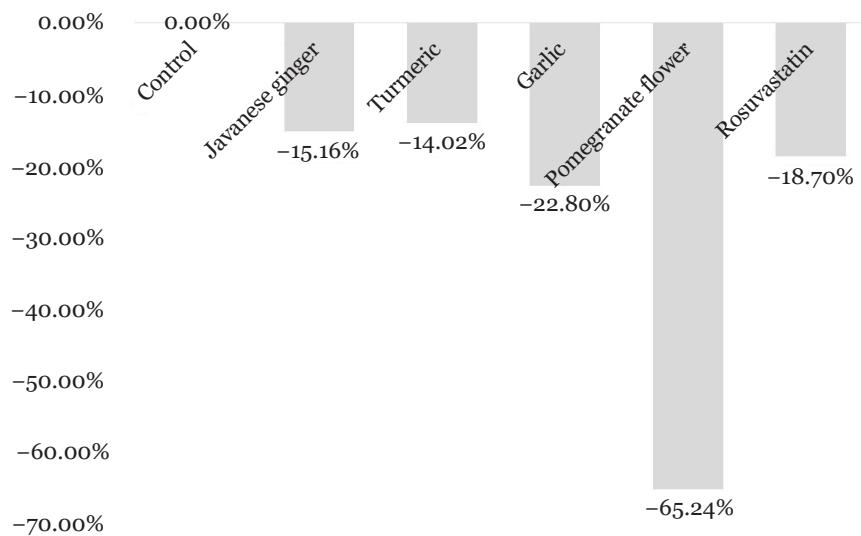
Figure 2   Percentage Reduction in Total-C Compared to Controls

Table 2   LSD Test Results in Lowering Total-C Data of the Six Treatment Group

	Control 0.00%	**Javanese Ginger** −15.16%	**Turmeric** −14.02%	**Garlic** −22.80%	**Pomegranate Flower** −65.24%	**Rosuvastatin** −18.70%
Control		**	**	**	**	**
Javanese ginger			NS	*	**	NS
Turmeric				*	**	NS
Garlic					**	**
Pomegranate flower						**
Rosuvastatin						

Discussion

This study showed that garlic and pomegranate flowers lowered LDL-C compared to the control with a significant difference. The potential of pomegranate flowers in lowered LDL-C is better than rosuvastatin. The potential for garlic is equivalent to rosuvastatin which was used as a comparison. In addition, Javanese ginger, turmeric, garlic, and pomegranate flowers reduced total-C compared to controls with significant differences. The potential of garlic and pomegranate flowers in lowering total-C is better than rosuvastatin. The potential for Javanese ginger and turmeric is equivalent to rosuvastatin which was used as a comparison.

The test materials for this study consisted of Javanese ginger, turmeric, garlic, and pomegranate flowers, each of which had been previously studied. Here are some studies that have been done before. Previous research of Javanese ginger with a 560 mg/kg BW showed a decrease in LDL-C and increased HDL-C with experimental mice.[9] Research on herbal medicine containing *Cassia sennae* dried leaves, *Sonchus arvensis* dried leaves, *Guazuma ulmifolia* dried leaves, *C. longa* dried rhizomes, *C. xanthorrhiza* dried rhizomes, *Camellia sinensis* dried leaves, and *Phyllanthus niruri* dried herb in human research subjects have been done previously. This study showed a decrease in plasma cholesterol levels from 212.42 mg/dL to 196.6 mg/dL after

28 days of treatment.[4] The main content of Javanese ginger (*Curcuma xanthorhiza* Roxb.) is curcuminoid which in several studies has shown its role as an anti-hypercholesterolemic agent.[10]

The content of turmeric, which plays a role in reducing total cholesterol and LDL cholesterol, is curcumin. This main ingredient also has an antioxidant effect that maintains SOD activity.[11] Research using curcumin can lower total cholesterol and LDL cholesterol and reduce cardiovascular disease risk.[12] Curcuminoids are the main components, especially in turmeric, and the mechanism of action of turmeric is mainly through this curcumin. The pharmacological effects of curcuminoids include lowering cholesterol levels and also having a hypoglycemic effect.[13] Research on turmeric effects conducted on human research subjects showed that a turmeric dose of 1 gram/day for 28 days reduced total cholesterol from 234.44 mg/dL to 202.06 mg/dL.[14] Turmeric has anti-adipogenesis potential by inhibiting the synthesis of triglycerides and cholesterol and inhibiting fat droplet formation in HepG2 cells.[15] Another study with human research subjects, acute coronary syndrome patients, were administrating by low doses of curcumin showed a trend of decreasing total cholesterol and LDL cholesterol levels.[16] Turmeric is a yellow spice with curcumin as its active ingredient. Turmeric affects Akt, growth factor, NF-kB, metastatic and angiogenic pathways. Turmeric also modulates cancer cells in humans, lowers the risk of cardiovascular disease, and suppresses inflammatory reactions. Turmeric also has antimicrobial, anti-obesity, prevents tumor formation, has antidepressant and anti-anxiety effects.[17]

Garlic has been used as a medicinal plant for thousands of years. Research shows garlic reduces total cholesterol levels by 7% and LDL cholesterol by 0.01% compared to controls.[18] Garlic is known as an agent used for the prevention and treatment of cardiovascular diseases and metabolic diseases such as diabetes, dyslipidemia, and hypertension. Research has shown that the active ingredient of garlic, allicin, can reduce cholesterol, thereby reducing the risk of disease due to atherosclerosis.[19] Garlic has active content, namely sulfur compounds, such as S-allyl cysteine, alliin, ajoene, and diallyl disulfide. This active ingredient has pharmacological effects. Some of the pharmacological effects of garlic include reducing the risk of cardiovascular disease, having antimicrobial, antioxidant effects, and reducing cancer risk. Previous research has shown that garlic lowers total cholesterol and LDL cholesterol but has no effect on HDL cholesterol and triglycerides.[20] Garlic with a dose of 900 mg/day reduces total cholesterol and LDL cholesterol. Garlic can also be used for the prevention of oral thrush in children.[21] Research on the effects of garlic with human research subjects in a village in Surabaya shows that consumption of four grams of garlic can reduce cholesterol levels and is recommended for hypercholesterolemia patients as a complementary therapy.[22]

Previous research has shown that consumption of pomegranate juice reduces LDL cholesterol and reduces oxidized LDL. The results showed reduced cholesterol accumulation in the cells and fewer foam cells.[23] Pomegranate has antioxidant activity, both in infusion and in the form of ethanol extract.[24] Previous research shows that giving pomegranate ethanol extract at a dose of 30 mg/200 g BW/day for 15 days reduces LDL cholesterol levels.[25]

Conclusions

The conclusion is that garlic and pomegranate flowers lowered LDL-C and total-C, while Javanese ginger, turmeric, garlic, and pomegranate flowers reduced total-C.

Conflict of Interest

The authors have read the manuscript and agreed to submit it in its current form for publication in the journal. There are no conflicts of interest to declare.

Acknowledgment

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RESEARCH ARTICLE

Characteristics of Patients with Type 2 Diabetes Mellitus in Al-Ihsan Regional General Hospital

Siti Annisa Devi Trusda,[1] Wida Purbaningsih,[2] Budiman,[3] Siti Salma Nurhaliza Fitriadi[4]

[1]Department of Biochemistry, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[2]Department of Histology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[3]Department of Public Health, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[4]Undergraduate Medical Study Program, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

The prevalence of type 2 diabetes mellitus (T2DM) in Indonesia is high, contributing to the fourth mortality rate for non-communicable diseases in Indonesia. The population of T2DM patients spread across all provinces, including West Java, which is the most populous province in Indonesia. One of the referral hospitals in West Java is Al-Ihsan Regional General Hospital in Bandung regency. The purpose of this study was to describe the characteristics of T2DM patients who came to Al-Ihsan Regional General Hospital according to age, gender, and comorbidities parameters. It was a descriptive cross-sectional study using secondary data from medical records of T2DM patients between January 2017 and November 2020. The results were the highest prevalence and incidence of T2DM were in 2017 with as many as 5,051 and 653 respectively; the highest gender each year was female, range between 584–3,333, with the highest male: female ratio of 1:2 in 2017; the age group with the highest prevalence was 55–65 years which was 3,468 (39.53%); and top five comorbidities were hypertension (35.68%), cataracts (6.01%), osteoarthritis (3.58%), pulmonary tuberculosis (2.92%) and dyspepsia (2.91%). This study concluded that the prevalence and incidence of T2DM in Al-Ihsan Regional General Hospital were high, with the predominant female patients, elderly, and comorbid hypertension.

Keywords: Age group, characteristics, comorbid, gender, T2DM

Karakteristik Pasien Diabetes Melitus Tipe 2 di RSUD Al-Ihsan

Abstrak

Angka kejadian diabetes melitus tipe 2 (DMT2) di Indonesia cukup tinggi, menyumbangkan angka kematian keempat penyakit tidak menular di Indonesia. Penderita DMT2 tersebar di seluruh provinsi, termasuk Jawa Barat yang merupakan provinsi terpadat di Indonesia. Salah satu rumah sakit rujukan di Jawa Barat adalah RSUD Al-Ihsan di Kabupaten Bandung. Tujuan penelitian ini adalah menggambarkan karakteristik pasien DMT2 yang datang ke RSUD Al-Ihsan dilihat dari usia, jenis kelamin, dan komorbid. Penelitian ini merupakan penelitian deskriptif *cross-sectional* menggunakan data sekunder berupa rekam medis pasien DMT2 periode Januari 2017 hingga November 2020. Didapatkan bahwa prevalensi dan insidensi DMT2 tertinggi pada tahun 2017 sebesar 5.051 dan 653 masing-masing; jenis kelamin terbanyak pada setiap tahun adalah wanita sebesar 584–3.333 dengan rasio pria:wanita tertinggi 1:2 pada tahun 2017; kelompok usia dengan prevalensi tertinggi adalah 55–65 tahun sebesar 3.468 (39,53%); dan lima komorbid tertinggi adalah hipertensi (35,68%), katarak (6,01%), osteoartritis (3,58%), tuberkulosis paru (2,92%), dan dispepsia (2,91%). Simpulan penelitian ini adalah prevalensi dan insidensi DMT2 di RSUD Al-Ihsan tinggi dengan pasien terbanyak wanita, lanjut usia, dan komorbid hipertensi.

Kata kunci: DMT2, jenis kelamin, karakteristik, kelompok usia, komorbid

Introduction

Like several other Asian countries, Indonesia has a high incidence of type 2 diabetes mellitus (T2DM). Based on data from the International Diabetes Federation (IDF),[1] Indonesia is on diabetes alert status because it is in seventh place in the top 10 countries or territories for number of adults (20–79 years) with diabetes in 2019 and 2030. The prevalence of patients with diabetes in Indonesia reaches 6.2%, which means that more than 10.8 million people had diabetes in 2020. The mortality rate due to diabetes in Indonesia is in the fourth position after cancer, stroke, and kidney disease.[2,3] T2DM patients are distributed across all provinces in Indonesia, and the highest distribution is on the island of Java.[2]

West Java is the most populated province in Indonesia, with a DM prevalence of 1.28% of its 49.94 million population, i.e., 639,232 people.[3,4] Several hospitals in West Java have become referral centers for T2DM patients, including the Al-Ihsan Regional General Hospital West Java Province in Bandung regency. Therefore, this study aimed to describe the incidence, prevalence, and characteristics of the T2DM patients based on gender, age group, and comorbidities in Al-Ihsan Regional General Hospital within the year 2017–2020 (four years) period.

Methods

It was a cross-sectional study using secondary data sourced from outpatient medical records of T2DM patients of Al-Ihsan Regional General Hospital West Java Province between January 2017 and November 2020. The data were tabulated and grouped based on gender, age group, and comorbidities.

The Health Research Ethics Committee of the Universitas Islam Bandung has approved this research, with the ethical approval number: 093/ KEPK-Unisba/X/2020.

Results

From 8,773 T2DM patients admitted to the Outpatient Department of Al-Ihsan Regional General Hospital for four years, the highest number of patients was in 2017 (5,051) and the least in 2020 (936). The incidence in each year ranges from 502 (in 2019) to 653 (in 2017). However, the number of new cases in 2017 was only 12.93% compared to all patients in that year, while in fact, the year with the highest percentage of new cases was in 2020, which is 54.27% (Figure).

In all years of study, T2DM was more prevalent in females than males. The highest prevalence of females was in 2017 which was 3,333 patients, with the highest ratio also in 2017 which was 1:2, while the lowest prevalence in 2020 as many as 584 patients, and the lowest ratio was in 2019 which was 3:5 (Table 1).

From Table 2, we may observe that the age group 55–65 years is the age group with
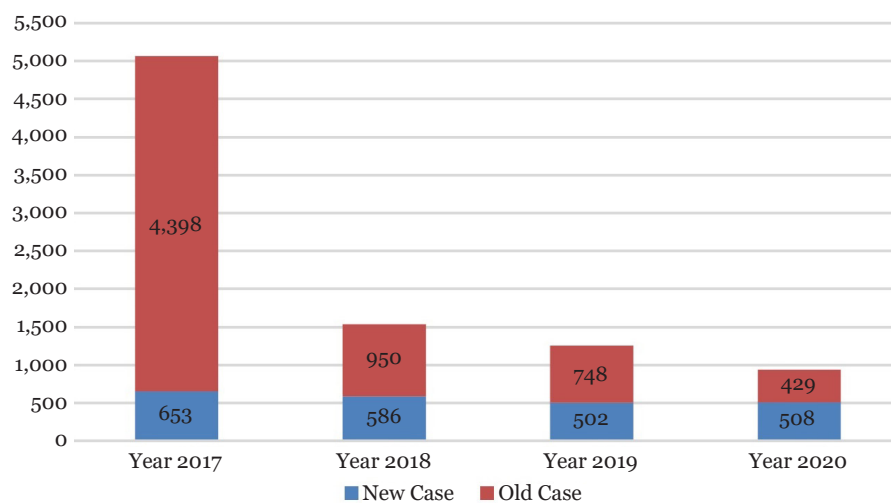
Figure Incidence and Prevalence of T2DM over Four Years of Study
Showing a large composition of old cases visiting the outpatient department in 2017, and a high incidence of T2DM in 2020 compared with all cases in that year

the highest incidence of T2DM in all years of observation (39.53%), followed by the age group 45–54 years (29.10%).

Top 15 highest comorbid changes every year, but in all years of observation, hypertension is always the first most comorbid, it was the highest in 2017 at 48.71% and the lowest in 2020 at 14.06%. The distribution of comorbid in each year can be seen in Table 3, while a summary of the top 5 comorbid of all years can be seen in Table 4.

Discussion

In general, the incidence of T2DM each year is relatively even, ranging from 502–653. It is consistent with IDF predictions that in Southeast Asia, there is a tendency to increase the incidence by 74% from 2019 to 2030.[1] This means that T2DM is a non-communicable disease that still needs to be observed. Prevention is even more encouraged, in this case, efforts to improve lifestyle.[5]

The highest prevalence of T2DM was seen in 2017 but decreased drastically in the following years. Whether this situation was caused by mortality, or due to decreased patient compliance, or switching treatment to another hospital/treatment center, still needs further investigation. The high prevalence of T2DM in

Asian countries, most of which are developing countries, is related to several things, including urbanization, rapid economic growth, changes in lifestyle and diet, and also: aging.[6,7]

The population of Bandung regency, which is the coverage area of Al-Ihsan Regional General Hospital, is a developing urban area. Cultural changes, including diet and lifestyle, and stressful life such as increasing living standards, long working hours, rush hours can increase stress, all of which are a risk of prediabetes.[8–10]

From Figure, we can observe that the lowest prevalence was in 2020. This situation was most likely due to patient restrictions related to the COVID-19 pandemic, which reduced patient visits. More than half (53%) of the 155 countries globally have partially or entirely disrupted services for hypertension treatment; 49%, 42%, and 31% for diabetes and diabetes-related complications treatment; cancer treatment, and cardiovascular emergencies, respectively.[11] However, as shown in Figure 1, the incidence of T2DM, when compared to its prevalence, is the highest in 2020. As we all know, at the beginning of 2020, the whole world experienced a COVID-19 pandemic, and we were all forced to adapt to this situation. The existence of lockdown, work from home, school from home, and other online activities causes sedentary behavior, which in turn leads to weight gain, which is one of the risk

Table 1 Characteristics of T2DM Patients in Outpatient Department Al-Ihsan Regional General Hospital

Gender	2017	2018	2019	2020	Σ
Male (M)	1,732	590	505	355	3,182
Female (F)	3,333	946	751	584	5,614
Ratio M:F	1:2	3:5	2:3	3:5	1:2.1

Table 2 Age Distribution of T2DM Patients in Outpatient Department Al-Ihsan Regional General Hospital

Age Distribution (Years)	2017	2018	2019	2020	Σ	%
10–24	29	23	15	14	81	0.92
25–44	399	171	170	131	871	9.93
45–54	1,406	483	367	305	2,561	29.19
55–65	2,106	557	467	338	3,468	39.53
66–74	828	229	188	108	1,353	15.42
75–90	277	72	43	39	431	4.91
>90	6	1	0	1	8	0.09

Table 3 Top 15 Comorbid of T2DM in Al-Ihsan Regional General Hospital

No.	2017	n	%	2018	n	%	2019	n	%	2020	n	%
1	Hypertension	2,467	48.71	Hypertension	292	19.01	Hypertension	247	19.67	Hypertension	132	14.06
2	Osteoarthritis	192	3.79	Cataract	112	7.29	Diabetic foot ulcer	62	4.94	Diabetic foot ulcer	70	7.45
3	Cataract	177	3.49	Diabetic foot ulcer	53	3.45	Osteoarthritis	40	3.18	ESRD	46	4.90
4	Dyspepsia	149	2.94	Dyspepsia	50	3.26	Dyspepsia	35	2.79	Pulmonary TB	27	2.88
5	Mononeuropathy	82	1.62	Osteoarthritis	28	1.82	Coronary artery disease	33	2.63	CKD grade I	23	2.45
6	Diabetic foot ulcer	62	1.22	Retinal disorder	22	1.43	Cataract	29	2.31	Dyspepsia	22	2.34
7	Kidney disorder	35	0.69	CKD grade I	16	1.04	CKD grade I	19	1.51	Coronary artery disease	17	1.81
8	Pulmonary TB	24	0.47	Mononeuropathy	14	0.91	Polyneuropathy	18	1.43	GERD	15	1.60
9	Coronary artery disease	21	0.41	Polyneuropathy	13	0.85	Pulmonary TB	13	1.04	Heart failure	13	1.38
10	Unspecified asthma	21	0.41	Heart failure	13	0.85	Retinal disorder	13	1.04	Osteoarthritis	13	1.38
11	Heart failure	20	0.39	Pulmonary TB	11	0.72	GERD	11	0.88	Polyneuropathy	12	1.28
12	Retinal disorder	15	0.30	Coronary artery disease	9	0.59	Cellulitis	9	0.72	Cataract	11	1.17
13	Acute URTI	15	0.30	Acute gastritis	8	0.52	Stroke	8	0.64	Mononeuropathy	10	1.06
14	Hyperlipidemia	11	0.22	Hyperlipidemia	7	0.46	Pneumonia	8	0.64	Retinal disorder	8	0.85
15	Polyneuropathy	8	0.16	Nontoxic goiter	5	0.33	Lumbar radiculopathy	7	0.56	Presbyopia	8	0.85

Table 4 Five Most Common Comorbid in Patients with T2DM

No.	Comorbid	n	%
1	Hypertension	3,138	35.68
2	Cataract	529	6.01
3	Osteoarthritis	315	3.58
4	Pulmonary tuberculosis	257	2.92
5	Dyspepsia	256	2.91

factors for T2DM.[12,13]

In addition, restrictions on hospital services, delays in elective and palliative care, insufficient staff and closure of hospital services, transportation restrictions due to lockdown have caused people to postpone appointments with their doctors, making it too late to prevent T2DM that happens in almost all countries.[14–16]

In the results of this study, it was found that the prevalence of female T2DM patients was higher male in all years of observation, despite the ratio of the male and female population in Bandung regency and West Java where Al-Ihsan Regional General Hospital located was 1:1.[4,17] Similar result also occurred in studies in Mexico, Kerala India, and Saudi Arabia, where the prevalence of T2DM was higher in women.[18–20]

A pre-existing theory states that males tend to be at higher risk for T2DM, associated with a higher visceral fat distribution (2:1). However, total fat in females is higher, distributed in other parts of the body, i.e., subcutaneous and gynoid fat. The relationship between visceral fat and the risk of insulin resistance is well established.[21,22]

The explanation of the results of this study that differs from the theory is that in females, there are certain risks related to reproductive factors and reproductive history. Women with early menarche, irregular menstrual cycles, polycystic ovary syndrome (high androgen levels), and a history of gestational diabetes increase the risk of T2DM later in life.[23] In addition, female patients are more compliant to treatment and more aware of their body condition, so more females come to the treatment center.[24,25]

The highest incidence of T2DM was in the 55–65 age group (39.53%), although the increase began to be seen in the 45–54 age group (29.19%).

This result is consistent with the results obtained in Mexico, India, Saudi Arabia, and China, which found that the highest incidence of T2DM was in the age group above 45 years.[6,18-20] The average onset of T2DM is at the age of 45 years. This onset is influenced by the interplay between modifiable and nonmodifiable factors and genetic and environmental factors. Obesity, characterized by an increase in BMI and waist circumference, low physical activity, high sedentary behavior, and socioeconomic status, are modifiable factors. In contrast, ethnicity, family history with T2DM, puberty, low birth weight, previous gestational diabetes are nonmodifiable factors.[26,27] These conditions begin long before the onset of DM and progress to a condition known as prediabetes and metabolic syndrome. The state of prediabetes can begin at the age of young adults around 25–34 years (prevalence pre-DM in Arabic), some even as early as 18 y.o. (CDC) (prevalence pre-DM in the USA), with a peak prevalence at 45–64 years (CDC). This situation is still reversible if lifestyle modifications are made, especially physical activity and diet.[5]

Prediabetes is when the plasma glucose is elevated above normal range but below clinical diabetes, manifested as either impaired fasting glucose or impaired glucose tolerance. Prediabetes commonly becomes the underlying cause of metabolic syndrome. Both, in turn, are closely associated with obesity or vice versa.[28]

The persistence condition of prediabetes and metabolic syndrome leads to T2DM development, and many studies predict that from the onset of prediabetes to progress to diabetes, the average time required is about 2.49 to less than ten years.[5,29] This fact is according to the age group with the highest prevalence of T2DM, i.e., 55–65 years.

From Table 4, we can see that T2DM patients have hypertension as the most common comorbid, followed by cataracts, osteoarthritis, pulmonary TB, and functional dyspepsia. Hypertension is also the most common comorbid in Saudi Arabia, China, Bangladesh, Pakistan, and Srilanka.[30-33]

The presence of hypertension in T2DM can occur before or after T2DM itself. Before T2DM, there was low-grade chronic inflammation whose mediators were released into the circulation, initiating the process of atherosclerosis which ended in narrowing of blood vessel diameter, which resulted in increased peripheral resistance and hypertension.[34,35]

In T2DM patients, an increase in blood pressure is closely related to elevated peripheral resistance due to vascular remodeling and an increase in vascular volume due to hyperinsulinemia and hyperglycemia caused by insulin resistance.[36]

Cataract was the second most common comorbid after hypertension (Table 4). In other studies, the prevalence of cataracts in T2DM patients also ranged from 40–60%.[37,38] In DM patients, there is the polyol pathway activation, which causes the aldose reductase enzyme to convert glucose into sorbitol. Aldose reductase in cataract formation plays an important role as an initiation factor. Intracellular accumulation of sorbitol will cause osmotic changes, resulting in hydropic lens fibers, which then degenerate and form cataracts. In the lens, the production of sorbitol occurs more rapidly than its conversion to fructose by the enzyme sorbitol dehydrogenase, and it is more difficult to remove this sorbitol by diffusion. The accumulated sorbitol creates a hyperosmotic state so that fluid moves inward to balance the osmotic gradient, then collapse and liquefaction of lens fibers occur, leading to the formation of lens opacity.[34,35,39,40]

Osteoarthritis (OA) was the third most common comorbid; following previous studies, almost half (47–52%) of T2DM patients have some form of arthritis.[41,42] The relationship between diabetes mellitus and OA has been confirmed in several studies. T2DM has a pathogenic effect on OA through several pathways: a) chronic hyperglycemia, which induces oxidative stress, overproduction of proinflammatory cytokines and AGEs in joint tissue; b) insulin resistance, which can both act locally and causes a systemic low-grade inflammatory state; c) leptin, which causes chondrocyte apoptosis while increasing MMP and cytokine production from chondrocytes; d) increased FFA associated obesity and insulin resistance may also modulate the development of OA; e) GLUT-1, the amount is increased in the plasma membrane of joint cells and chondrocytes, thereby increasing glucose uptake in hyperglycemic conditions, causing the production of IL-1β, TGF-β1, and MMP—oxidative stress, and AGEs which ultimately leads to OA.[41-44]

The close relationship between TB and DM has long been known. Evidence that DM is often comorbid for TB and vice versa has also been confirmed.[45] In this study, it was found that TB became the 4th comorbid with 257 patients or 2.92% of all patients studied. This result is in line with research in Jember, East Java, which even

shows the TB-DM rate is higher than Indonesia in general.[46]

Mycobacterium tuberculosis (*M.tb*) immunity is dysfunctional in DM patients, with an exaggerated and delayed response.[47] Monocytes from DM patients had a significantly decreased association in binding and phagocytosis of *M.tb*. This defect affects the changes in serum monocytes and opsonins for *M.tb*, especially the C3 component that mediates *M.tb* phagocytosis. DM patients also found it delayed innate immunity to *M.tb* due to delayed delivery of *M.tb*-bearing APCs to lymph nodes that drain the lungs. Similarly, it was found that levels of the inflammatory cytokines interleukin-6 and interleukin-17 were significantly increased in T2DM patients, which correlated with increased oxidative stress. This situation causes a downstream effect, where there is a decrease in interleukin-12, which plays a role in activating NK cells and differentiating and activating CD4^{+} T cells, which play a role in resistance to intracellular microorganisms (*M.tb*).[47,48]

In the study results, dyspepsia was the fifth most common comorbid of T2DM patients, with 2.91%. These manifestations are typically due to gastroparesis. Gastroparesis is a syndrome characterized by slowed gastric emptying without the mechanical obstruction of the stomach, often found in patients with diabetes >10 years and microvascular complications. Despite the controlled blood sugar, this condition persists and is stable for 12–25 years. The cardinal symptoms are postprandial fullness, nausea, vomiting, and bloating.[49,50]

DM patients may exhibit diabetic autonomic neuropathy (DAN). Autonomic nerves are prone to metabolic attacks because they are unmyelinated. DAN affects several organ systems, including the gastrointestinal system, causing gastroparesis with manifestations similar to dyspepsia.[49]

As many as 5–12% of DM patients experience gastroparesis with variations in prevalence up to 24–30% in a different center.[51,52] The possible pathophysiology of gastroparesis is associated with poor glycemic control, sympathetic vagal neuropathy, Cajal interstitial cell abnormalities, and loss of neuronal nitric oxide synthase.[50]

Conclusions

The prevalence and incidence of T2DM in Al-Ihsan General Regional Hospital were high, with the predominant female patients, highest age group were in the elderly, and hypertension as the most common comorbid.

Conflict of Interest

The authors have no conflict of interest to declare.

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RESEARCH ARTICLE

Relationship between Vitamin B9 (Folic Acid), Vitamin B12 (Cobalamin), and Peripheral Neuropathy in Children with Beta-Thalassemia Major

Uni Gamayani,[1] Titin Junaidi,[1] Nushrotul Lailiyya,[1] Nur Suryawan,[2] Nanan Sekarwana[2]

[1]Department of Neurology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, [2]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Vitamin B9 (folic acid) and B12 (cobalamin) are essential vitamins that play roles in the process of hematopoiesis and maintaining the function of peripheral nerves. Therefore, these deficiencies may create a risk for peripheral neuropathy in beta-thalassemia major patients. The purpose of this study is to determine the relationship between vitamin B9 level, vitamin B12 level, and peripheral neuropathy in beta-thalassemia major children. It was an observational analytical study with a case-control design has been conducted at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, in May–July 2019. There were 47 beta-thalassemia major children with peripheral neuropathy (case) and 41 healthy children (control). All subjects completed a general demographic questionnaire, underwent neurological examination, and were tested for vitamin B9 and B12 serum levels. Data were then analyzed using the unpaired t test to compare the vitamin levels between both groups and Spearman's rank correlation test to investigate the correlation between vitamin levels and the number of affected nerves in the case group. Comparison of folic acid levels in the case group (21.52 ± 6.22 ng/mL) and the control group (23.81 ± 7.51 ng/mL) showed no significant difference (p=0.19). In contrast, cobalamin in the case group (288.57 ± 168.61 ng/mL) and the control group (385.95 ± 197.48 ng/mL) showed a significant difference (p=0.01). In addition, there was a moderate correlation (p=0.004, r=0.41) between folic acid level and the number of motoric nerves affected in the case group. In conclusion, cobalamin level correlates with peripheral neuropathy in beta-thalassemia major patients, and folic acid level correlates with the number of affected nerves, especially motoric nerves.

Keywords: Cobalamin, folate, peripheral neuropathy, thalassemia

Hubungan antara Vitamin B9 (Asam Folat), Vitamin B12 (Kobalamin), dan Neuropati Perifer pada Anak dengan Talasemia Beta Mayor

Abstrak

Vitamin B9 (asam folat) dan B12 (kobalamin) merupakan vitamin esensial yang berperan dalam proses hematopoesis dan menjaga fungsi saraf tepi. Defisiensi vitamin ini dapat menimbulkan risiko neuropati perifer pada pasien talasemia beta mayor. Tujuan penelitian ini mengetahui hubungan antara kadar vitamin B9, vitamin B12, dan neuropati perifer pada anak talasemia beta mayor. Metode penelitian ini adalah analitik observasional dengan rancangan studi kasus kontrol yang dilakukan di RSUP Dr. Hasan Sadikin Bandung, Indonesia pada Mei–Juli 2019. Terdapat 47 anak talasemia beta mayor dengan neuropati perifer (kelompok kasus) dan 41 anak sehat (kelompok kontrol). Seluruh subjek penelitian mengisi kuesioner demografi umum, menjalani pemeriksaan fisis neurologis, serta dilakukan tes kadar vitamin B9 dan B12 serum. Uji t test tidak berpasangan digunakan untuk membandingkan kadar vitamin pada kedua kelompok dan uji korelasi Spearman untuk membandingkan kadar kedua vitamin tersebut dengan jumlah saraf yang terkena pada kelompok kasus. Perbandingan kadar asam folat kelompok kasus ($21,52\pm6,22$ ng/mL) dengan kelompok kontrol ($23,81\pm7,51$ ng/mL) menunjukkan perbedaan yang tidak bermakna (p=0,19), sedangkan perbandingan kadar kobalamin kelompok kasus ($288,57\pm168,61$ ng/mL) dengan kelompok kontrol ($385,95\pm197,48$ ng/mL) menunjukkan perbedaan yang bermakna (p=0,01). Selain itu, terdapat korelasi sedang (p=0,004; r=0,41) antara kadar asam folat dan jumlah saraf motorik yang terkena pada kelompok kasus. Kesimpulan, kadar kobalamin berhubungan dengan neuropati perifer pada penderita talasemia beta mayor dan kadar asam folat berhubungan dengan jumlah saraf yang terkena, terutama saraf motorik.

Kata kunci: Folat, kobalamin, neuropati perifer, talasemia

Correspondence: Dr. Uni Gamayani, dr., Sp.S.(K). Department of Neurology, Faculty of Medicine, Universitas Padjadjaran/ Dr. Hasan Sadikin General Hospital. Jln. Pasteur No. 38, Bandung 40161, West Java, Indonesia. E-mail: gamayani@yahoo.com

Introduction

Vitamin B, especially are vitamin B1 (thiamine), B6 (pyridoxine), B9 (folic acid), and B12 (cobalamin), has the function of maintaining the development and integrity of the nervous system, especially the peripheral nervous system.[1,2] Thalassemia is a hereditary blood disorder in the form of impaired synthesis of alpha or beta-globin chains, with beta-thalassemia major as the most severe clinical form.[3] Indonesia is one of the countries included in the thalassemia areas, with the number of carriers reaching 5–10%. West Java, as the most populated province in Indonesia, currently has approximately 445 people with beta-thalassemia.[4,5]

The life expectancy of people with thalassemia increases with the availability of routine blood transfusions and iron chelation therapy. It also means that the possibility that they experience complications also increases. Neurological complications experienced by these patients may affect central and peripheral nerves. Several neurological disorders have been reported in the peripheral nervous system, one of which is peripheral neuropathy.[6,7]

Peripheral neuropathy is a neurological complication with a reasonably high incidence with symptoms often missed by the patients, especially in younger patients. It is not included in one of the focuses in the management of children with thalassemia.[7] With age, peripheral neuropathy symptoms will worsen and interfere with daily activities, thus reducing the quality of life of the patients, especially when accompanied by neuropathic pain. Therefore, it is necessary to evaluate peripheral nerves in thalassemia patients to provide appropriate interventions to maintain the quality of life of people with thalassemia.[8] Nerve conduction study, or NCS, is an electrophysiological examination that can detect disorders of the peripheral nerves, both in motor and sensory nerves, and helps to establish the diagnosis of peripheral neuropathy. This type of examination is necessary because peripheral neuropathy is often subclinical. Abnormal NCS images can also be found in people who have not shown symptoms and or signs of neuropathy, making it useful for early detection of peripheral nerve disorders in patients with beta-thalassemia major.[6]

Peripheral neuropathy in people with thalassemia can be caused by various etiologies, including anemia, high ferritin level, and vitamin B deficiency. In 2015, there were 447 children with beta-thalassemia major undergoing blood transfusions at the Thalassemia Clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia. Dewi et al.[9] in 2017 and Gamayani et al.[10] in 2019 investigated the incidence of peripheral neuropathy in thalassemia patients treated at Dr. Hasan Sadikin General Hospital. Dewi et al.[9] studied 50 beta-thalassemia major patients aged 8–14 years and discovered that hemoglobin and ferritin levels are linked to 98 percent of peripheral neuropathy features in the Nerve Conduction Study (NCS). In 2019, Gamayani et al.[10] showed that persistent anemia and iron deposition are related to a significant peripheral neuropathy prevalence in adult patients. However, those previous studies did not examine cobalamin and folic acid levels, that those levels were unknown in their study subjects. Based on the description of the background above, the purpose of this study is to determine the relationship between vitamin B9 (folic acid), vitamin B12 (cobalamin), and peripheral neuropathy in beta-thalassemia major children.

Methods

This study used a case-control approach to study children with beta-thalassemia major presented to the Pediatric Thalassemia Clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia, who met the inclusion and exclusion criteria. Subjects included were children aged 8–18 years, diagnosed with peripheral neuropathy based on NCS examination, had a mean pre-transfusion Hb level of <10 g/dL with a mean serum ferritin level of 1,000 µg/L in the last six months, had normal nutritional status according to the WHO's body mass index, and children and parents were willing to participate in the study.

Subjects in the control group were of the same age as the subjects in the case group. However, they were not diagnosed with peripheral neuropathy based on anamnesis and physical examination and had hemoglobin and ferritin levels within normal limits. Exclusion criteria for both case and control groups were the presence of hearing loss, visual disturbances, neurological deficits leading to suspicion of an intracranial lesion. In addition, they had a history of chronic infectious disease, had a history of autoimmune disease or malignancy, and had a history of using

drugs that cause peripheral neuropathy such as chemotherapy agents (vincristine) or tuberculosis drugs (isoniazid). This study was performed from May to August 2019 and approved by the Universitas Padjadjaran Research Ethics Committee through the issuance of ethical clearance number: 588/UN6.KEP/EC/2019.

Data on the characteristics of the subjects were obtained from medical records, anamnesis, physical and laboratory examinations, and NCS examination results from the neurophysiology laboratory of the hospital. Data collected were then processed using SPSS for Windows version 24.00. Both groups were tested using the unpaired t test to compare the vitamin levels between both groups and Spearman's rank correlation test to investigate the correlation between vitamin levels and the number of affected nerves in the case group. The relationship was considered significant if the p value was ≤0.05.

Results

Forty-seven children were included in this study as the case subjects with characteristics as listed in Table 1. Sensory symptoms resulting from history taking were reported in five individuals (11%) and included numbness, discomfort, and tingling. There were no motor complaints found. Four participants (7%) had sensory impairments in the form of glove and stocking hypesthesia, as determined by neurological testing. There was no evidence of a motor deficiency, on the other hand. In eight patients, physiological responses were found to be reduced (17%).

Table 1 presents the description of the characteristics of the case group subjects based on age, gender, motor and sensory symptoms, and the number of affected nerves based on NCS examination. The mean age of the case group was 13.27±1.79 years, with more or less equal gender distribution between males and females. Based on the previous NCS examination, the average number of sensory nerves affected from the six nerves examined was 1.44±1.79. In comparison, examination on eight motor nerves demonstrated that more than 3.04±1.81 nerves were affected.

The control group in this study consisted of 41 healthy children. The comparison of the characteristics between the case and control groups is listed in Table 2. Table 2 describes the comparison between the characteristics of the

Table 1 Case Group Characteristics

Characteristics	Mean±SD	n=47 (%)
Age (year)	13.27±1.79	
Gender		
Male		26 (55)
Female		21 (45)
Sensory symptoms		
Yes		5 (11)
No		42 (89)
Motor symptoms		
Yes		0 (0)
No		47 (0)
Abnormal NCS results		
Sensory		
Yes		47 (100)
No		0 (0)
Motor		
Yes		47 (100)
No		0(0)
Number of abnormal nerves based on NCS		
Sensory	1.44±1.79	
Motor	3.04±1.81	

Table 2 Comparison of Case and Control Group Characteristics

Characteristics	Case(n=47)	Control (n=41)	p Value
Age (year)			0.710
Mean±SD	13.27±1.79	13.19±1.77	
Median	13.00	13.00	
Range (min–max)	10.00–17.00	11.00–18.00	
Gender			0.940
Male	26 (55%)	23 (56%)	
Female	21 (45%)	18 (44%)	
Folic acid/vitamin B9 levels (ng/mL)			0.190
Mean±SD	21.52±6.22	23.81±7.51	
Median	20.70	21.90	
Range (min–max	11.90–41.50	12.50–43.30	
Cobalamin/vitamin B12 levels (ng/mL)			0.010[*]
Mean±SD	288.57±168.61	385.95±197.48	
Median	252.60	324.20	
Range (min–max)	98.40–792.40	100.10–871.30	

Note: [*]p value<0.05 significant

case and control groups based on age, sex, folic acid levels, and cobalamin levels. There was no significant difference in age, sex, and folic acid levels between the two groups. In contrast, a significant difference was seen in the cobalamin level.

Table 3 demonstrates that there was a significant correlation between the folic acid level and the number of motor nerves affected. Table 4 demonstrates that there was no correlation between cobalamin level and the number of nerves affected.

Discussion

Subjects of this study were 8–18 years old, making it possible to do accurate anamnesis and neurological examination. No significant differences in gender, age, and BMI between case and control subjects were found; hence, the two groups were deemed comparable.

A ferritin level serum of >1,000 g/L and Hb<10 g/dL are considered the most common factors that cause long-term complications in thalassemia patients undergoing regular

Table 3 Correlation between Folic Acid Level and Number of Affected Sensory and Motor Nerves based on NCS in Case Group

Variables	Correlation	R	p Value
Folic acid level and number of sensory nerves affected	Spearman	0.157	0.293
Folic acid level and number of motor nerves affected	Spearman	0.41	0.004

Table 4 Correlation between Cobalamin Level and Number of Affected Sensory and Motor Nerves based on NCS in Case Group

Variables	Correlation	R	p Value
Correlation between cobalamin and number of sensory nerves affected	Spearman	0.237	0.109
Correlation between cobalamin and number of motor nerves affected	Spearman	0.137	0.359

transfusion and iron chelation treatment.[11] Peripheral neuropathy is one of the complications that can occur in this condition.[12] Decreased folic acid and cobalamin levels can be observed due to increased demand or high degradation of ferritin, which may become one of the causes of peripheral neuropathy.[13-15]

Vitamins B1, B6, folate, and B12 are micronutrients known to play essential roles in maintaining peripheral nerves. The mechanism of action of these vitamins is closely related, especially between folate and B12. These two vitamins should be examined simultaneously because they are related to the "remethylation pathway" process. Vitamin B12 is needed by the body to convert N5-methylene THF to THF. If there is a vitamin B12 deficiency, THF will be trapped in the form of N5-methylene THF, or known as "folate trapping," which causes folate deficiency.[16] In this study, the levels of other B vitamins were not examined; thus, they become the confounding factor in the study.[2,16]

Folic acid levels were within normal limits among subjects in the case group of this study. There was no case of folic acid deficiency, and no significant difference was identified in folic acid levels between the case and control groups. It is different from the study by Patil and Mujawar[17] on 30 thalassemia patients and Asma et al.[18] on 145 thalassemia patients. In Asma et al.[18] study, the folic acid deficiency was seen in 10.3% of the subjects. This difference may be because the case group subjects in our study had taken folic acid supplements for a period of 3 to 14 years at a dose of 3 to 5 tablets/day or 3 to 5 mg/day with good adherence, while this is not clear in the study of Asma et al.[18]

Serum folic acid level examination is performed as an initial screening when deficiency is suspected; however, it does not reflect the long-term folic acid status. Folic acid concentration will increase five times from the normal value after four hours of oral intake of 1.6 mg folic acid supplement. In addition, serum folic acid levels can also be used as a marker of supplement intake.[19] This study selected serum folic acid to be examined because it is easier and more efficient to work in bulk when compared to the red blood cell folic acid. There was a significant difference in cobalamin level between the case and control group, but the levels in both groups were still within normal limits.

This study found a significant relationship between folic acid level and the number of motor nerves affected. The higher the folic acid level was, the lesser the number of motor nerves affected. This follows the findings of Kang et al.[20] stated that folic acid has a neurotrophic effect on myelin differentiation, proliferation, and repair by regulating the methylation process of deoxyribonucleic acid (DNA) in specific genes. It increases Schwann cells proliferation and migration and secretion of nerve growth factor (NGF) required for myelin repair.[21] Sensory nerve regeneration is faster because it has >1 Schwann cell. In contrast, motor nerves regenerate more slowly because it is a myelinated nerve type with a larger axon size with only one Schwan cell.[22] Thus, folic acid levels are more significant in motor nerves when compared to sensory nerves.

Folic acid and cobalamin have an essential role in maintaining peripheral nerves. The two vitamins work together and are closely related. Cobalamin is a cofactor that plays an essential role in the folate cycle by converting N5-methylene-tetrahydrofolate (N5-methylene-THF) into the active form of folate, tetrahydrofolate (THF). When cobalamin deficiency occurs, folate will be trapped in the form of N5-methylene-THF, which is known as "folate trapping".[11]

Folic acid and cobalamin play a role in the homocysteine metabolism process, which is an amino acid. The methionine metabolism may become toxic when it takes reactive oxygen species (ROS) that can cause nerve damage, especially in myelin.[23] Cobalamin deficiency is established by examining a low serum cobalamin level of <200 ng/mL. Cobalamin levels in the subjects of this study were within normal limits. They were not associated with the presence of peripheral neuropathy nor the number of affected nerve fibers on NCS examination. A previous study by Asma et al.[18] on 157 beta-thalassemia patients demonstrated that 28.6% of these patients experienced cobalamin deficiency.

This study did not include examinations of the levels of other B vitamins such as vitamins B1 and B6, which also play a role in peripheral neuropathy.

Conclusions

No relationship between folic acid level, cobalamin level, and peripheral neuropathy was identified in children with beta-thalassemia major in this study. However, there is a relationship between

folic acid level and the number of motor nerves affected based on the NCS examination.

Conflict of Interest

All authors declare no conflict of interest.

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RESEARCH ARTICLE

Association of Chest X-Rays Features with the Length of Stay in Suspected COVID-19 Status

Zulmansyah,[1,2] Gaga Irawan Nugraha,[3] Dwi Agustian,[4] Dida Akhmad Gurnida[5]
[1]Doctoral Study Program of Medical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia,
[2]Department of Child Health, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[3]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia,
[4]Department of Public Health, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia,
[5]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/
Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Coronavirus disease 2019 (COVID-19) is a new type of respiratory infection that first emerged in December 2019 in Wuhan, Hubei, China. COVID-19 is caused by a new variant of virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Examining the chest x-rays is one technique to diagnose COVID-19. This study aims to determine the association of chest x-rays features in suspected COVID-19 patients with the length of stay at Al-Ihsan Regional General Hospital West Java Province and Banten Regional General Hospital in June–November 2020. The subject was 29 COVID-19 people were confirmed, whereas 31 people were not. The statistical analysis used Pearson correlation and multi-linear regression. This study found that tuberculosis had a strong association with length of stay (p value=0.048, association=0.4), and also there is a robust association between bilateral pneumonia and duration of stay (p value=0.028, association=0.873). A linear regression model discovery of TB chest x-rays on the subject raises the treatment by 0.5867 days. In addition, the discovery of bilateral pneumonia increases the length of stay of treatment by 0.32218 days more than the discovery of unilateral pneumonia. In general, tuberculosis, bacterial pneumonia, viral pneumonia, and bilateral pneumonia together affected the outcome of length of stay of patients with suspected COVID-19.

Keywords: Chest x-rays, COVID-19, diagnosis of COVID-19, length of stay

Asosiasi Gambaran Rontgen Toraks terhadap Lama Rawat pada Pasien Suspek COVID-19

Abstrak

Coronavirus disease 2019 (COVID-19) adalah jenis infeksi saluran pernapasan baru yang pertama kali mewabah pada Desember 2019 di Wuhan, Hubei, Cina. COVID-19 disebabkan oleh varian virus baru yang disebut *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). Pemeriksaan rontgen toraks merupakan salah satu teknik mendiagnosis COVID-19. Penelitian ini bertujuan mengetahui asosiasi gambaran rontgen toraks pada pasien suspek COVID-19 dengan lama rawat inap di RSUD Al-Ihsan Provinsi Jawa Barat dan RSUD Banten pada Juni–November 2020. Subjek penelitian adalah 29 orang terkonfirmasi COVID-19 dan 31 orang tidak. Analisis statistik menggunakan korelasi Pearson dan regresi multilinier. Penelitian ini menemukan bahwa tuberkulosis memiliki hubungan yang kuat dengan lama perawatan (p=0,048; asosiasi=0,4) dan juga terdapat hubungan yang kuat antara pneumonia bilateral dan lama perawatan (p=0,028; asosiasi=0,873). Penemuan model regresi linier rontgent toraks TB pada subjek meningkatkan risiko perawatan 0,5867 hari lebih lama. Selain itu, penemuan pneumonia bilateral meningkatkan risiko perawatan 0,32218 hari lebih lama dibanding dengan penemuan pneumonia unilateral. Secara umum, tuberkulosis, pneumonia bakteri, pneumonia viral, dan pneumonia bilateral secara bersama-sama berpengaruh terhadap luaran lama rawat inap pasien suspek COVID-19.

Kata kunci: COVID-19, diagnosis COVID-19, lama rawat, rontgen toraks

Introduction

Coronavirus disease 2019 (COVID-19) is a new variant of respiratory tract infection that first appeared in Wuhan, Hubei, China, in December 2019. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a novel kind of virus. COVID-19 was declared a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) on January 30, 2020, and its status was later renewed to the pandemic.[1] There were 120,417,285 cases reported until March 15, 2021, with 1,419,455 cases reported in Indonesia, resulting in 38,426 deaths.[2]

Systemic symptoms (fever, malaise, weakness, headache, myalgia), respiratory symptoms (cough, runny nose, shortness of breath), or other symptoms (diarrhea, nausea, vomiting) are all used to conduct the COVID-19 test. Ground glass opacity, unilateral or bilateral lesions, and pneumonia can also be seen on chest x-rays.[3] Abnormalities in chest x-rays are generally distributed bilaterally. The heart, lungs, respiratory tract, blood arteries, and lymph nodes are some of the common signs found in chest x-rays. The spine and chest, including the ribs, collarbones, and the top of your spine, can also be seen in chest x-rays.[4] The appearance of chest x-rays that are commonly found in COVID-19 patients is diffuse or patchy asymmetric opacity such as pneumonia caused by other types of coronavirus, such as the Middle East respiratory syndrome (MERS).[5]

Chest x-rays are commonly used checks to detect diseases such as COVID-19. Bilateral/multilobular pneumonia distribution is commonly found in patients with COVID-19. Bilateral pneumonia is inflammation that can injure the lungs. Types of pneumonia can affect both the lungs and makes the tissue around the air sacs of this vital organ irritated.[6] The COVID-19 pandemic effects provide significant challenges to viral pneumonia, bacterial pneumonia, and pulmonary tuberculosis (TB) control initiatives, primarily by obstructing pneumonia, bacterial pneumonia, TB diagnosis, and treatment. Because the symptoms of tuberculosis and COVID-19 are so similar, countries with a shaky diagnostic infrastructure struggle to distinguish between the two infections; this problem harms therapeutic decision-making and, as a result, in the prognosis of both diseases.[7]

The link between chest x-rays in COVID-19 patients has not been demonstrated to date. Nonetheless, a better understanding of the association between these causes and disease prognosis is critical in offering the proper treatment for ill patients and delaying disease development. Furthermore, these variables can help forecast the results of COVID-19 suspected and confirmed positive events. Therefore, this study aimed to correlate chest x-rays features in suspected COVID-19 patients with the length of stay.

Methods

This research started on June to November 2020; patients were treated at Al-Ihsan Regional General Hospital West Java Province, Bandung, and Banten Regional Hospital, Banten, West Java, Indonesia with the following signs of respiratory tract infection: 1) a high fever (above 38°C); 2) respiratory problems such as cough, runny nose, shortness of breath, sore throat, or confirmed positive for pneumonia. Based on a definitive clinical image, there is no other explanation. In addition, the patient may have: 1) a history of traveling or staying in an environment where COVID-19 transmission has been registered, or 2) interaction with offenders and confirmed positives.

The patient was admitted to the radiology center for x-rays one day after admission to the hospital. The diagnosis is divided into pulmonary tuberculosis, bacterial pneumonia, viral pneumonia, and non-pneumonia findings based on x-ray findings (pleural effusion, infiltration, lesion, and others. The impacted areas are also divided into two categories: bilateral and unilateral pneumonia. The statistical analysis used Pearson correlation and multi-linear regression.

Results

This study uses data from 60 COVID-19 patients divided into two groups: 29 positive patients COVID-19 and 31 non-confirmed COVID-19 patients (Table 1).

The average age is 48 years in both groups. Male are more in confirmed COVID-19 compared to non-COVID-19 groups. The COVID-19 group was double-folded by patients with comorbidities

Table 1 Subject Demographic

Variables	Value or Number of Patients		p Value
	COVID-19 (+) (n=29)	COVID-19 (−) (n=31)	
Age			
Year±standard deviation	48±10.3	48.6±20.4	0.880
Median (range)	47 (26–64)	47.5 (0–86)	
Gender			
Male	21	15	0.060
Female	8	16	0.060
Comorbidity			
Hypertension	7	4	0.270
Heart disease	3	1	0.760
Diabetes mellitus	2	1	0.530
Chest x-rays			
Bacterial pneumonia	16	20	0.599
Viral pneumonia	8	3	0.110
Tuberculosis	5	8	0.350
Bilateral	14	6	0.040

than the COVID-19 (−) group, but the results were not significant. In comparison, chest x-ray found a significant difference between the subject of COVID-19 and COVID-19 (−) in bilateral pneumonia of 0.040.

Having tuberculosis has a strong association with length of stay. It means it will take longer if the subject has TB in the chest x-ray. Bilateral pneumonia has a very strong level of association. It means if the subject has bilateral pneumonia, the length of stay will be longer.

According to the results for the confounding variable, the level of correlation in the age group and diabetes mellitus is very low. In addition, gender, hypertensive comorbidity, and heart disease all have low levels of association.

The results of the regression analysis (Table 4.) If TB chest x-ray are discovered, the length of stay is increased by 0.5867 days. The second discovery of bilateral pneumonia chest x-ray increases the length of stay by 0.32218 days more than a unilateral pneumonia chest x-ray discovery.

Discussion

This study found a significant difference between the subject of COVID-19 and COVID-19 (−) 19 in bilateral pneumonia chest x-rays of p=0.040. Aside from that, there is a very strong association between bilateral pneumonia and length of stay (p value=0.028, association=0,873). If

Table 2 Length of Stay in COVID-19 Subgroup

Dependent Variable	Independent Variables	COVID-19 (+)	COVID-19 (−)	Total	p Value
Length of stay	Bacterial pneumonia	21	17	38	0.032
	Viral pneumonia	8	3	11	0.989
	Tuberculosis	16	13	29	0.048
	Bilateral	14	6	20	0.028
	Confounding variables				
	Comorbidity				
	Hypertension	7	4	11	0.012
	Heart disease	3	1	4	0.032
	Diabetes mellitus	2	1	3	0.038

Table 3 Length of Stay Association in COVID-19 Subgroup

Dependent Variable	Independent Variables	p Value	Association	Level Association
Length of stay	Bacterial pneumonia	0.032	0.254	Low
	Viral pneumonia	0.989	0.005	Very low
	Tuberculosis	0.048	0.400	Strong
	Bilateral	0.028	0.873	Very strong
	Confounding variables			
	Age	0.673	0.058	Very low
	Gender	0.104	0.322	Low
	Comorbidity			
	Hypertension	0.012	0.207	Low
	Heart disease	0.032	0.230	Low
	Diabetes mellitus	0.038	0.118	Very low

there is a bilateral pneumonia chest x-rays, the length of stay will be increased by 0.32218 days. These results are following other studies; severe bilateral pneumonia can trigger the formation of scars. This condition makes the lung tissue stiff, shortness of breath, until the breath failure which results in a length of stay the patient is getting longer. There was only one necessary chest radiograph, including bilateral pneumonia observations. The positive COVID group had slightly more bilateral pneumonia anomalies on chest radiographs (50%) than the COVID-negative subject group (21.4%). According to Bao et al.,[8] most COVID-19 patients had bilateral pneumonia manifestations of lesions, especially bilateral lower lobes. The rate of occurrence was 78.2 percent (95% CI=65.69–88.19).[8] COVID-19 pneumonia was overwhelmingly bilateral on the chest x-ray 72.9% of the time, based on a comprehensive meta-analysis of 2,847 patients in China and Australia and a global descriptive analysis of 39 case report articles summarizing 127 patients (95% CI=58.6–87.1).[2] Lomoro et al.[9] studied 32 patients with COVID-19 disease and discovered bilateral lung anomalies (78.1%). Bilateral pneumonia was the most common

finding on chest radiographs.[10–13]

Tuberculosis has a strong association with length of stay (p value=0.048, association=0.4). It means it will take longer if the subject has TB in chest x-rays. If TB thorax photographs are discovered, the length of stay is increased by 0.5867 days. TB increases the severity to COVID-19 of its symptoms. Nonetheless, certain substantial limitations of this study should be mentioned, such as its small sample size and the lack of clinical criteria to define the presence of tuberculosis.[14] Another study from the Philippines confirmed TB's negative impact on COVID-19, linking the co-infection to a higher risk of morbidity and mortality.[15] However, the most significant evidence of the impact of tuberculosis on COVID-19 prognosis came from a South African cohort study. Data from almost 3 million patients treated by the public health system, with or without COVID-19, were compared, accounting for the presence of other comorbidities such as TB and HIV. The findings show that patients infected with COVID-19 are more likely to die if they had a previous history of TB.[16]

The study outcomes show that tuberculosis

Table 4 Length of Stay Regression Results

Variables	Parameter Symbol	Coefficient	Standard Error	p Value
Constant	β_0	5.6957	0.27447	0.0003
Thorax photo				
Tuberculosis	β_5	0.5867	0.0823	<0.00001
Bilateral pneumonia	β_6	0.32218	0.0853	0.0002

Note: *significant if the p value<0.05

increases vulnerability to COVID-19 and contributes to the severity of its symptoms subgroup. Individuals who are socially vulnerable or who have comorbidities have a worse prognosis. On the other hand, there is still no information about the impact of SARS-CoV-2 on the advancement of tuberculosis. With the evidence of a possible synergism between *M. tuberculosis* and the new coronavirus, such as the severity of symptoms and co-infection sequelae, it is clear that more practical research into the TB/COVID-19 pathophysiology is required.[7]

Conclusions

The discovery of TB chest x-rays on the subject raises the risk of the length of treatment. In addition, the discovery of bilateral pneumonia chest x-rays increases the risk of the length of treatment more than the discovery of unilateral pneumonia chest x-rays. Thus, in general, tuberculosis, bacterial pneumonia, viral pneumonia, and bilateral pneumonia together affected the outcome of length of stay of patients with suspected COVID-19.

Conflict of Interest

There is not any conflict of interest in this research.

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